IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

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Plaintiff,

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TEVA PHARMACEUTICALS USA and TEVA PHARMACEUTICAL INDUSTRIES LTD.

Civil Action No. 06-89 (GMS)

Defendants.

DECLARATION OF CYNTHIA LAMBERT HARDMAN, ESQ. IN SUPPORT OF THE MOTION OF DEFENDANTS TEVA PHARMACEUTICALS USA, INC. AND TEVA PHARMACEUTICAL INDUSTRIES LTD. TO TRANSFER VENUE TO THE SOUTHERN DISTRICT OF NEW YORK PURSUANT TO 28 U.S.C. § 1404(A)

- I. Cynthia Lambert Hardman, Esq., hereby declare as follows:
- I am an attorney-at-law of the state of New York and an associate of the law firm 1. of Kenyon & Kenyon LLP, counsel, together with Morris, James, Hitchens & Williams LLP, for defendants Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") (collectively, "Teva") in this action. I make this Declaration in support of Teva's Motion to Transfer Venue to the Southern District of New York Pursuant to 28 U.S.C. § 1404(a).
- Kenyon & Kenyon LLP is counsel to Teva USA in Teva Pharmaceuticals USA, 2. Inc. v. Pfizer Inc., 03cv7423 and 04cv4979 (LAP) (consolidated), which is pending in the United States District Court for the Southern District of New York (the "New York Action"). A true and correct copy of the complaints in that action, which were filed on September 22, 2003 and June 24, 2004, respectively, are attached hereto as Exhibits A and B. The New York Action is assigned to Judge Loretta A. Preska.

- In the New York Action, Pfizer Inc. ("Pfizer") moved to dismiss the complaints 3. for lack of subject matter jurisdiction. Pfizer subsequently brought counterclaims against Teva USA for infringement of U.S. Patent Nos. 5,605,889 (the "889 patent") and 6,268,489 (the "'489 patent"). Attached hereto as Exhibits C and D, respectively, are true and correct copies of Pfizer's Answers in case nos. 03cv7423 and 04cv4979.
- Before substantial discovery had taken place in the New York Action, Pfizer 4. granted Teva USA a covenant not to sue with respect to the '889 patent. The terms of the covenant have not been made public. Attached hereto as Exhibit E is a true and correct copy of a submission to the United States Patent and Trademark Office ("PTO") during reissue proceedings for the '889 patent, in which Pfizer disclosed the covenant to the PTO.
- On June 20, 2005, Teva USA filed a Consolidated Amended Complaint in the 5. New York Action. Pfizer's Answer to that complaint, which it filed on July 15, 2005, included a counterclaim against Teva USA for infringement of the '489 patent. Teva USA's Consolidated Amended Complaint and Pfizer's Answer were filed under seal pursuant to the Protective Order issued in that action, and therefore copies of these documents are not attached.
- On September 23, 2005, the parties in the New York Action filed summary 6. judgment motions. In support of their summary judgment motions, Teva USA and Pfizer submitted declarations from ten experts, including experts in polymorphism, x-ray crystallography, organic chemistry, drug formulation, solid-state nuclear magnetic resonance spectroscopy, and infrared and Raman spectroscopy. These declarations were all filed under seal, and their contents are subject to the Protective Order in the New York Action. The topics covered in the declarations include, among other things, the compound azithromycin and its crystalline forms; the crystalline form of the API used in Teva's azithromycin products; the

research, development, composition, formulation, manufacture, testing and labeling of Teva's azithromycin products; the analytical techniques used to identify and quantify crystalline forms in general, and crystalline forms of azithromycin in particular, including x-ray crystallography, infrared and Raman spectroscopy and solid state nuclear magnetic resonance spectroscopy; and the scientific theories that attempt to explain when and why particular crystalline forms of compounds, including azithromycin, may be found in particular samples.

- 7. In late January 2006, counsel for Pfizer informed counsel for Teva USA that Pfizer had concluded that Teya's azithromycin tablets do not contain azithromycin dihydrate. Pfizer subsequently granted Teva USA a covenant not to sue with respect to the '489 patent. The terms of the covenant have not been made public.
- 8. In view of Pfizer's covenant on the '489 patent, Judge Preska denied as moot the parties' motions for summary judgment, but gave Teva USA permission to make an attorney's fees motion. Attached hereto as Exhibit F is a true and correct copy of Judge Preska's February 17, 2006 Order.
- 9. On February 14, 2006, Teva filed a declaratory judgment action against Pfizer in the Southern District of New York, Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. v. Pfizer Inc., 06cv1134. Attached hereto as Exhibit G is a true and correct copy of the Complaint in that case.
- Attached hereto as Exhibit H is a true and correct copy of a printout from Pfizer's 10. website, www.pfizer.com, which includes a list titled "Pfizer Locations."
- Attached hereto as Exhibit I are true and correct copies of submissions made by 11. Pfizer to the PTO during the prosecution of U.S. Patent No. 6,977,243.

12. According to Pfizer's submissions to the PTO, the inventors listed on the '243 patent reside in Quaker Hill, Connecticut and Stonington, Connecticut. Quaker Hill and Stonington are approximately 125 and 135 miles, respectively, from the Southern District of New York, and approximately 254 and 264 miles, respectively, from the District of Delaware.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Executed on <u>Feb. 23</u> 2006.

CERTIFICATE OF SERVICE

I hereby certify that on the 23rd day of February, 2006, I electronically filed the foregoing document, DECLARATION OF CYNTHIA LAMBERT HARDMAN, ESQ. IN SUPPORT OF THE MOTION OF DEFENDANTS TEVA PHARMACEUTICALS USA, INC. AND TEVA PHARMACEUTICAL INDUSTRIES LTD. TO TRANSFER VENUE TO THE SOUTHERN DISTRICT OF NEW YORK PURSUANT TO 28 U.S.C. § 1404 (a), with the

Clerk of the Court using CM/ECF which will send notification of such filing to the following:

Rudolf E. Hutz, Esq. Daniel C. Mulveny, Esq. Connolly Bove Lodge & Hutz LLP 1007 North Orange Street Wilmington, DE 19801

Additionally, I hereby certify that on the 23rd day of February, 2006, the foregoing document was served as indicated:

VIA HAND DELIVERY

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EXHIBIT A

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	U.S.D.C. S.D. N.Y. CASHIERS
Civil Action No.	CASHIERS
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COMPLAINT FOR DECLARATORY JUDGME

Plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), for its Complaint against Pfizer Inc. ("Pfizer"), alleges as follows:

THE PARTIES

- Teva is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090. Teva is a developer, manufacturer, and marketer of generic pharmaceutical products in the United States.
- On information and belief, Pfizer is a Delaware corporation with its principal place of business at 235 East 42nd Street, New York, New York, 10017-5575.
- 3. On information and belief, Pfizer owns U.S. Patent No. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," a copy of which is attached hereto as Exhibit A.
- 4. On information and belief, Pfizer owns U.S. Patent No. 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," a copy of which is attached hereto as Exhibit B.

On information and belief, Pfizer holds New Drug Application ("NDA") No. 50-5. 711 for ZITHROMAX[®] 250 mg azithromycin dihydrate ("azithromycin") tablets, and NDA No. 50-730 for ZITHROMAX® 600 mg azithromycin tablets.

JURISDICTION AND VENUE

- This Court has original jurisdiction over the subject matter of this action pursuant 6. to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 et seq.
- This Court may declare the rights and other legal relations of the parties pursuant 7. to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction seeking a declaratory judgment that the '889 and '489 patents are invalid and not infringed.
- Personal jurisdiction exists over the defendant because defendant has its principal 8. place of business within this district, and because defendant does business within this district.
 - 9. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and 1400(b).

THE PRESENCE OF AN ACTUAL CONTROVERSY

- ZITHROMAX [®] is an oral antibiotic. In its 2002 Annual Report, Pfizer states that 10. in 2002, sales of ZITHROMAX totaled \$1.5 billion.
- Teva holds Abbreviated New Drug Application ("ANDA") Numbers 65-153, 11. filed December 12, 2002, and 65-150, filed November 27, 2002. These ANDAs are directed to a generic version of ZITHROMAX and have been accepted by the U.S. Food and Drug Administration ("FDA") for review. By preparing and filing these ANDAs, Teva has made

substantial preparation to make, use, import, offer to sell, and sell a generic version of ZITHROMAX on the U.S.

- On information and belief, Pfizer's '889 and '489 patents contain claims directed 12. to azithromycin, a component of ZITHROMAX®, and Pfizer would therefore assert the '889 and '489 patents against Teva for alleged infringement of those patents if Teva commercially marketed generic versions of ZITHROMAX® tablets.
- Pfizer has demonstrated a willingness and intention to enforce foreign patents that 13. are related to ZITHROMAX 9. Pfizer brought suit in Canada against Novopharm, an affiliate of Teva, asserting the Canadian equivalent to the '489 patent. Pfizer Canada and Pfizer Inc. v. Novopharm, Federal Court - Trial Division, Ontario, Court File No. T-74-03.
- Pfizer has refused to grant Teva a covenant that it will not enforce the '889 and 14. '489 patents against Teva. On August 5, 2003, Teva hand delivered to Pfizer a letter requesting such a covenant. Teva requested that Pfizer respond to the letter within forty five days of receipt. To date, Teva has received no response from Pfizer. Teva's August 5, 2003 letter to Pfizer is attached hereto as Exhibit C.
- Pfizer (or its predecessor) has also demonstrated its intention to protect other 15. products from generic competition by Teva. On at least five occasions, Pfizer sued or maintained suit against Teva (or its related entities) for patent infringement relating to other drugs for which Teva has filed an ANDA: (i) Pfizer Inc. and Pfizer Technologies Ltd. v. Novopharm Ltd., 00-cv-01475 (N.D. Ill.), concerning fluconazole; (ii) Pfizer Inc./Warner-Lambert v. Teva, 00-cv-4589 and 00-cv-4168 (D.N.J.), concerning gabapentin; (iii) Schwarz Pharma, Inc., Schwarz Pharma AG and Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc., 01-cv-4995 (D.N.J.), concerning moexipril; (iv) Bayer and Pfizer v. Biovail & Teva, 01-cv-

1205 and 01-cv-1206 (D.P.R.), concerning nifedipine; and (v) Warner-Lambert v. Teva USA, 99cv-0922 (D.N.J.), concerning quinipril.

- Based upon Pfizer's refusal to covenant to not enforce the '889 and '489 patents 16. against Teva, Pfizer's suit against Teva's affiliate to enforce the Canadian equivalent of the '489 patent, and Pfizer's pattern of aggressively enforcing its patents to attempt to prevent generic competition by Teva, Teva is under a reasonable apprehension that Pfizer will sue Teva, alleging infringement of the '889 and '489 patents.
- To avoid legal uncertainty and to protect its substantial investment (and 17. anticipated future investments) in its manufacturing process for its generic ZITHROMAX® product, Teva has instituted this declaratory judgment action.

COUNT I DECLARATORY JUDGMENT OF NONINFRINGEMENT

Teva's manufacture, use, offer for sale, sale, or importation of an FDA-approved 18. generic version of ZITHROMAX® does not, and would not, infringe any properly construed claim of the '889 patent.

COUNT II DECLARATORY JUDGMENT OF NONINFRINGEMENT

Teva's manufacture, use, offer for sale, sale, or importation of an FDA-approved 19. generic version of ZITHROMAX [®] does not, and would not, infringe any properly construed claim of the '489 patent.

COUNT III DECLARATORY JUDGMENT OF PATENT INVALIDITY

20. The claims of the '889 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

COUNT IV DECLARATORY JUDGMENT OF PATENT INVALIDITY

21. The claims of the '489 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

PRAYER FOR RELIEF

WHEREFORE, Teva respectfully requests the Court enter judgment against Pfizer to include:

- A. A declaration that Teva's manufacture, use or sale of Teva's generic version of ZITHROMAX will not infringe United States Patent No. 5,605,889;
- B. A declaration that Teva's manufacture, use or sale of Teva's generic version of ZITHROMAX will not infringe United States Patent No. 6,268,489;
 - C. A declaration that United States Patent No. 5,605,889 is invalid;
 - D. A declaration that United States Patent No. 6,268,489 is invalid;
- E. An award of Teva's reasonable costs and attorneys' fees in connection with this action; and

All such other and further relief as the Court may deem just and proper. F.

Dated: 9/22/03

By:

Steven J. Lee (SL1043)

Respectfully submitted,

Elizabeth J. Holland (EH0850)

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TEVA PHARMACEUTICALS USA, INC.

TXHIBITA

US005605889A

United States Patent [19]

Curatolo et al.

[11] Patent Number:

5,605,889

[45] Date of Patent:

Feb. 25, 1997

[54] METHOD OF ADMINISTERING AZITHROMYCIN

[75] Inventors: William J. Curatale, Niantic; George H. Foulds, Waterford, both of Conn.; Hylar L. Friedman, Bratileboro, VL

[73] Assignee: Pfixer Inc., New York, N.Y.

[21] Appl. No.; 235,069

[56]

[22] Filed; Apr. 29, 1994

[S1] Int. CL. A61K 31/79; A61K 9/14; A61K 9/20

C1. 514/29, 514/960; 424/464; 424/465; 424/474; 424/480; 424/481; 536/7.2 [52] U.S. CL

[58] Fleid of Search 514/29, 960; 536/7.2; 424/464, 465, 474, 480, 481

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CA Abstracts: vol. 120:38194a; 1994.

Zithromax (Trademark of Pfizer, Inc.) Capsules Package inact for azithromycin capsule douage form sold commercially in U.S.

Primary Examiner-John Kight Assistant Examiner-Howard C. Lee Attorney, Agent, or Firm-Peter C. Richardson; Gregg C. Benson; James T. Jones

ABSTRACT

An oral desage form of száthromycin which does not exhibit an adverse food effect; Specific azithromycin oral dosage forms including tablets, powders for oral suspensions and unit dose packets; Methods of treating microbial infections with the dosage forms; And the superatic packages containing the douge forms.

99 Claims, No Drawings

METHOD OF ADMINISTERING AZFIHROMYCIN

This invention relates to a dosago form of szithromycin, and also to a method of treating a microbial infection which involves administering szithromycin in the fed state to a mammal, including a human patient, in need of such treatment.

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 9a-aza9a-methyl-9-douto-9a-homoerythromycin A, a broad spectrum artimicrobial compound derived from crythromycin A.
Azithromycin was independently discovered by Bright, U.S.
Azithromycin was independently discovered by Bright, U.S.
No. 4,474,768 and Kobrehel et al., U.S. Pat. No.
4,517,359. These patents disclose that azithromycin and
certain derivatives thereof possess ambacterial properties
and are accordingly useful as antibiotics.

In general, it is known that the absorption and bioavail- 20 ability of any particular therapeutic agent can be affected by numerous factors when dosed orally. Such factors include the presence of food in the gustrointestinal (GI) tract because, in general, the gustric residence time of a drug is usually significantly longer in the presence of food than in 25 the fasted state. If the blogvailability of a drug is affected beyond a certain point due to the presence of food in the GI tract, the drug is said to exhibit a "food effect". Food effects are important insumuch as, when a drug exhibits an adverse food effect, there is risk associated with administering it to 30 a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remediate the condition for which the drug was administered.

Other factors can also be involved in drug bioavailability, the following being a non-comprehensive listing:

- (1) The particular desage form can affect bioavailability. For example, the gastric residence time of a tablet or capsule can be significantly longer than that of a suspension, and the difference may vary depending on whether the subject has eaten or is fasted.
- (2) The pH of the atomach varies, between the fed and fasted state, with the amount of food therein, and drugs which are decomposition-sensitive to pH can be affected accordingly.
- (3) The capacity of the liver to metabolize an absorbed drug (so-called "first pass" metabolism) may vary with the type of meal exten. For couragle some vegotables (such as brussels sprouts) can stimulate first pass metabolism of some drugs, but not others. Grapefruit juice, on the other hand, may inhibit first pass metabolism of some drugs.
- (4) Bile, which is released from the gallbladder into the small intestine when a meal is ingested, has the ability to solubilize poorly soluble drogs and thus increase bioavailability.

Additional factors can also be involved in the absorption and bioavailability of a particular drug, and absorption can actually be increased as well as decreased. These additional 60 factors include, for example, pH-dependent solubility, site-specific intestinal parmeation rate, instability to insestinal enzymes, susceptibility to first pass metabolism, and instability to colonic bacteria. Given the plethora of factors which can influence bioavailability, there unually is no way to 65 predict, in the absence of actual testing, whether a particular drug will exhibit a food effect. For example, Toothaker and

2

Welling, Ann. Rev. Pharmacol. Taxical., 1980, 173-99, discuss various drugs whose absorption is delayed in the presence of food (cephalexin, cedealor, metronidazole, aspirin, alciofenae, indoprolen, digoxin, cimetidine), whose absorption may be unaffected by food (ampicillin, erythromycin catalate, spiramycin, propylthiouracil, oxazepam, bendrufiumethiazide), and whose absorption is increased in the presence of food (crythromycin ethylsuccinate, nitrofurnatein, 8-methoxsalen, propramolol, metoprolol, dicoumarol, diazepam, hydrochlorothiazide).

As a further example, there appears to be no clear or definitive support for the proposition that tablets might exhibit fewer food effects than capsules, or vice-versa. Thothaker and Welling review studies which demonstrate food related reduced absorption for tablet dosage forms of erythromycin stearase, aspirin, nafelliin, and sotalol.

In the case of azithromycin, at least one (unpublished) study has shown that the absorption of azithromycin can be adversely affected if the patient is in a fed state, and it has heretofore been conventional wisdom that azithromycin capsule dosage forms exhibit a so-called adverse "food effect". Accordingly, in countries where azithromycin is currently available for use in the treatment of human patients, the product is sold with the specific direction that it be administered only in the fasted state, i.e. at least one hour before or two hours following a meal.

It would accordingly be useful if szithromycin could be administered to patients that have eaten recently and also if a dosage form for szithromycin were available which could be administered to patients that have eaten, as well as patients in a fasted state.

SUMMARY OF THE INVENTION

This invention provides an oral desage form of azithromycin which can be administered to a mammal (including humans) that has eaten and which exhibits substantially no adverse food effect, excluding any desage form which contains a significant amount of an alkaline earth notice or bydroxide. The desage form exhibits a mean (AUC_{nn}) (AUC_{nn}) of at least 0.80 with a lower 90% confidence limit of at least 0.75, the terms "(AUC_{nn})/(AUC_{nn})" and "90% confidence limit" being fully defined below.

In a further aspect, this invention provides a specific oral azithrumycin dosage form which does not exhibit an adverse food effect. The douge form comprises azithromycin and a harmacounically acceptable carrier, as bereinafter further detailed and described. The dosage form is in the form of a tablet (including both swallowable-only and chewable forms), in the form of a unit dose packet (sometimes referred to in the art as a "aschet"), in the form of a suspension made from a unit dose packet, in the form of a powder for oral suspension, and in the form of an oral suspension per se. It is noted that when a unit does packet is constituted, it is probably mainly in the form of a suspension if reconstituted according to directions, although the extent of suspension versus solution depends on a number of factors such as pH. The use of the term "cuspension" herein is intended to embrace liquids containing azithromycin partially in suspension and partially in solution, and also totally in solution.

In a further aspect, this invention provides a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits substantially no adverse food affect. The dosage form employed exhibits a

3

mean (AUC_{pa})/(AUC_{pa}) of at least 0.80 with a lower 90% confidence fimit of at least 0.75.

Reference herein and in the claims to a mammal (including humans) that has "caten" means that the mammal has eaten food of any sort within one hour prior to dosing up to 5 two hours after dosing.

In a further aspect, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithronycin which does not exhibit an adverse food effect contained therein, and, associated with said container, written matter non-limited as to whether the dosage form can be taken with or without food.

It is noted that powders for oral suspension and unit dose packets, of course, are not ingested directly by patients; rather, they are reconstituted in a suitable vehicle. These terms are nonetheless considered to be within the penumbra. 15 of the term "dosage form" for purposes of this invention.

Capsules as a dosage form do not form a part of the invention.

For purposes of this invention azithromycin may be administered alone or in combination with other therapeutic 20 arents.

A food effect can be detected and quantified as described, for example in Toothaker and Welling, supra, by determining the area under a curve (AUC) which plots the serum concentration (e.g., in µg/mL) of azithromycin along the 25 ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the values for AUC represent a number of values takes from all the subjects in a patient test population and are, therefore, mean values averaged over the emire test population. By measuring the area under the curve for a fed population of subjects (AUC_[x]) and comparing it with the area for the same population of fasted subjects (AUC_[x]), it can be determined whether a given drug exhibits an adverse food effect or not.

For definitional purposes of this invention, and specifically with respect to azithromycin dosage forms only, a 35 dosage form of azithromycin exhibits an adverse food effect if, after dosing a population, once fasted and once fed, the mean (AUC_{nn})/(AUC_{nn}) is below the value 0.80 and/or the lower 90% confidence limit for this ratio is below 0.75.

Convenely, a desage form of azithromycia which does 40 not exhibit an adverse food effect is one which, when assed on a test population, exhibits a value for (AUC, MAUC,) of at least 0.80 and a lower 90% confidence finit for this value of at least 0.75. The value for mean (AUC, MAUC,) can have any value above 0.80 and still be within the scope of this invention, though it is preferred that it have an upper (mean) limit of 1.25, with an upper 90% confidence limit of 1.40 or below.

A population of "fed" subjects, for purposes of definition and for measuring AUC_{pur} is one made up of subjects each 50 of whom has eaten a Food and Drug Administration (FDA)-recommended standard high fat breakfast within a period of twenty misutes, and then ingested (i.e., swallowed) the test dosage form easentially immediately thereafter. A standard high-fat breakfast consists of, for example, two eggs fried in 55 cm tablespoon of butter, two strips of bactor, six ounces of hash brown potatoes, two pieces of teast with two tearpoons of butter and two pats of jelly, and eight ounces of whole milk. This standard high-fat breakfast contains approximately 964 calories, 34% supplied as fat (58 gm) and 12% supplied as protein, calculated using the monograph "Nutritive Value of Foods", U.S. Department of Agriculture Home and Carden Bulletin Number 72. Additional food can also be consumed within the twenty minute period and the subject still qualifies as "fed". A "fasted subject" for purposes of definition and for measuring AUC_{pur} is one who has not eaten 65 for at least eight hours, typically overnight, prior to ingestion of the dosage form.

4

The 90% confidence limits on AUC, AUC, for a particular population, in this case either a fed or a fasted population, can be (and were) calculated as described following using Schairman's two one-sided test procedure.

The log-transformed AUCs were analyzed by means of an analysis of variance appropriate for a two-period, two-treatment crossover design. Analysis was carried out using Statinical Analysis System (SAS) software from SAS Institute, Cary, N.C. SAS procedure referred to in the SAS software as PROC GLM was used to determine sequence, subject within sequence, period and treatment (Fod/Fasted) effects. The sequence effect was tested using the [subject within sequence] mean square from the enalysis of variance (ANOVA) as an error term. All other effects were tested against residual error (error mean square) from the ANOVA. The LSMEANS statement of SAS was used to calculate the least aquere means and their standard errors and covariances. These were used to obtain estimates for adjusted differences between treatment means and standard errors associated with these differences (log transformed).

The 90% confidence interval for two-way crossover design was constructed, based on these estimates, as the difference plus (or minus) the standard error of the difference times the 93th percentile of the t-distribution with (twice the sample size-2) degrees of freedom. The smil-log was taken on the limits to obtain the corresponding confidence for the ratio.

That a doage form according to the invention does not exhibit an adverse food effect is surprising in view of the fact that azithromycin is unstable at low (acid) pH, on the order of the acidity encountered at the pH of stomach acid. The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus, without heing bound to any mechanism of action, it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention.

Commonly assigned co-pending application Set. No. 07/922,262 filed Jul. 30, 1992 discloses teste marking compositions of bitter pharmaceutical agents, such as available antibiotics, containing, as a taste-masking component, a basic compound selected from the group consisting of alkaline suth mides and alkaline earth hydroxides. A composition of this invention, if it contains an alkaline earth calde or hydroxide at all, contains less than a taste-masking amount of the taste-masking component. A composition of this invention therefore preferably contains less than about 1% of an alkaline earth caide or hydroxide, and may be free of such taste-masking component entirely.

DETAILED DESCRIPTION

Azithromycin is typically present in formulations according to the invention in an amount of from about 25 mg to about three grams, preferably 250 mg to two grams, for treatment of a human. If dosage forms are to be used for animal/veterinary applications, the amount can, of course, be adjusted to be outside these limits depending, for example, on the size of the animal subject being treated (e.g., a horse). The term "azithromycin" includes the pharmaceutically acceptable salts thereof, and also anhydrous as well as hydrated forms. The azithromycin is preferably present as the dihydrate, disclosed, for example, in published European Patent Application 0 298 650 A2.

In order to test whether a particular azithromycin dosago form exhibits an adverse food effect, the most schible method is accountly to test the dosage form in vive on a subject population, once fed and once fasted, determine the level of serum (or plasma) azithromycin with time, plot curves for the concentration of serum (or plasma) azithromycin with test of serum (or plasma) azithromycin with time, plot

5

mycin with time in each subject (fed and fasted) as described above, determine the area under each curve (conventionally, for example by simple integration) and finally determine whether the mean ratio (AUC_{tot})/(AUC_{tot}) exceeds 0.80, and whether the lower 90% confidence limit equals or exceeds 0.75.

It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithmonycin ready for dissolution in the they either provide azithromycin ready for dissolution in the GI tract essentially immediately following Ingestion (auspensions), or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution. While not wishing to be bound by theory, it is believed that if an azithromycin dosage form provides azithromycin immediately following ingestion for dissolution for the GI tract of the traction of the GI traction of the G tion in the GI tract, or at least provides azithromycin for dissolution within a certain time period following ingestion, the szidromycin will be absorbed into the bloodstream at a rate which results in substantially no adverse food effect. In order for an adequate rate of absorption to occur, it is believed that the dosage form should provide azithromycin at a rate such that at least about 90% of the azithromycin dissolves within about 30 minutes following ingestion, preferably within about 15 minutes following ingestion. A non-capsule dosage form comprising azithromycin is also considered to fall within the scope of the appended claims if 25 It satisfies the in vitro dissolution testing requirements enumerated herein. An azithromycin dosage form according to the invention exhibits at least about 90% dissolution of azithromycin within about 30 minutes, preferably within 15 minutes, when an amount of the desage form equivalent to 200 mg of szithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml approx. 0.1M dibasic sodium phosphate buffer, pH 6.0, 37° C. with paddles turning at 100 rpm. This test is described in US Pharmacopaea XXII, pp. 1578-1579. Dosage forms which 35 pass this test under more stringest conditions (lower volume patt less sex insies maye suringent tousingue tower temperature, of buffer, greater amount of dosage form, lower temperature, higher plf., lower paddle speed) are also included under the above definition. Any modifications to this test are also described herein. The time required for dissolution of a particular azilhromycin dosage form in this in vitro test is believed to be an indicator of the time required for disso-lution of the dosage form in the GI environment. The following discussion is believed pertinent in this record.

It is generally assumed and observed that the in vitro 45 diasolation rate of desage forms exhibits a mak order correlation with in vivo dissolation, particularly for a single desage form type, a.g. tablets, which vary systematically in composition. Thus in vitro dissolution evaluation serves an important role in control of the quality of manufactured desage forms. It is not necessarily true that the in vitro dissolution rate is exactly the same as the in vivo dissolution rate. This is not surprising, since the artificial conditions of an in vitro dissolution test (e.g. vessel geometry, stirring rate, stirring method, and so forth) are not klentical to the conditions under which a desage form disintegrates and dissolves in the CI tract.

When comparing desage forms of different type, e.g. capsules and tablets, in vitro dissolution rate should combate roughly with in vivo dissolution rate. However, subtle differences exist between the dissolution rate. However, subtle capsules and tablets. For expanles, at least partial dissolution of the gelatin shell must precede complete dissolution of the enclosed drug. Furthermore, capsule shells generally dissolve first at the capsule ends, and later at the capsule center. Tablets, on the other hand, disintegrate homogeneously. 65 Thus subtle differences may exist in the in virules vivo dissolution correlation when comparing capsules and tab-

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lets. For example, capsules and tablets which exhibit similar in vitro dissolution rates may exhibit subtle differences in in vivo dissolution rate. While such subtle differences may have so therapeutically significant effect on systemic bloavailability of an erally dosed drug, there are situations in which a significant effect may occur. For example, if a drug has the potential to exhibit an adverse food effect, drug-containing capsules and tablets which exhibit similar in vitro dissolution rates may actually differ with respect to whether an adverse food effect is observed when the dosage forms are orally dosed. In fact, this has been observed for arithromycin, as exemplified in the Raamples berein.

For the in vitro dissolution studies disclosed herein, azidnossycin was assayed by HPLC, utilizing a 5 micron alumina based hydrocarbonaceous spherical particle chromatographic column (15 cmod.4 cm), and a 5 micron alumina based hydrocarbonaceous spherical particle precolumn (5 cmod.4 cm) (both available from ES Industries, Markon, N.J.). A mobile phase consisting of 71% phosphate buffer/29% acetonirile (pH 11) was used, with electrochemical detection (e.g. Bloanalytical Systems, West Lafayette, Ind., LC.4B amperometric detector with dual series glassy extron electrodos).

Est in vitro food effect during them michanyanis in

For in vivo food effect studies, serum azithromycin is assayed using an HPLC assay described by R. M. Shepard et al. (1991) J. Chromatog. Biomed. Appl. 565, 321-337, with amparementic electocheraical detection. Alternatively, any assay method that produces equivalent results, for example, blossay, can be used.

Tablets according to the invention contain, as accessary ingredients, azithromycin and a disintegrant. Examples of tablet disintegrants are starch, progelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, crosslinked sodium carboxymethylcellulose (codium carboxymethylcellulose) (codium carboxymethylcellulose), microcrystalline cellulose (of the type available under the registered trademark Ac-Di-Sol) from FMC Corp. or the registered trademark from FMC Corp. Carmel, N.Y.), alginates, gunas, surfactants, effervescent mixtures, hydrous aluminum silicate, cross-linked polyvinylpymolidone (available commercially under the registered trademark PVP-XL from International Specialty Products, Inc.), and others as known in the art. Proferred disintegrants for arithromycin tablets are sodium croscarmellose (Ac-Di-Sol), sodium starch glycolate (available commercially under the registered trademarks Primojel from Avobe (Union, N.J.) or Generichem, (Little Falls, N.J.) and Exploitab from Mendell Corp.), microcrystalline cellulose (Avicel), and cross-linked polyvinylpymolidone (PVP-XL). Azithromycin tablets of this invention comprise arithromycin and 1–25% disintegrant, preferably 3–15% disintegrant based on total tablet weight. For example, a 463.5 mg tablet (250 mg activity azithromycin) may contain 9 mg sodium croscarmellose and 27 mg pregolationed asarch.

In addition to the active ingredient azithromycin and a disintegrant, tablets according to this invention may be formulated to optionally include a variety of conventional excipients, depending on the exact formulation, such as binders, flavorings, buffers, disease, colors, inbricants, sweetening agents, thickening agents, and gildants. Some excipients can serve multiple functions, for example as both binder and disintegrant.

Humples of binders are acacia, celiulose derivatives (auch as methyleellulose and bydroxypropyleellulose, bydroxypropyleellulose, bydroxypropyleellulose), gelarin, glucose, dextrose, xylitol, polymethycylulose, polyvinylpyrrolidose, atarch paste, sucrose, sorbitol, pregeistinized starch, gum tragacacth,

alginic acids and salts thereof such as acdium alginate, magnesium aluminum silicate, polyethylene glycol, guar gum, bentoektes, and the like. A preferred binder for acitromycin tablets is pregelatinized starch (available, for example, under the registered trademark Starch 1500, from Colorcon, Inc., West Point, Pa.).

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, entracts from plants leaves, flowers, fruits, and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, excalyptus, thyme oil, codar leaf oil, oil of natmeg, oil of sage, oil of bitter almonds, and cassia oil. Also useful as flavors are vanilla, cirus oil, including lemon, orange, grape, lime and grapefruit, and finit essences, including apple, banana, pear, peach, atrawherry, raspherry, chorty, plum, pheapple, apricot, and so forth. The smount of flavoring may depend on a number of factors including the organoleptic effect desired. Generally the flavoring will be present in an amount of from 0.5 to about 3.0 percent by used.

A variety of materials may be used as fillers or diluents. Busmples are spray-dried or subydrous lactose, successe, dextrose, maunitol, sorbitol, starch (e.g. starch 1500), cellulose (e.g. microcrystalline cellulose; Avicel), dihydrated or anhydrous dibasic calcium phosphate (available commercially under the registered trademark Emoompress from Meadell or A-Tab and Di-Tab from Rhone-Poulenc, Inc., Mommouth Junction, N.J.), calcium extremate, calcium sulfate, and others as known in the art.

Lubricants can also be employed herein in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants are magnesium stearate, stearic acid, glycerylbehaptate, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax from Union Carside, Inc., Danbury, Conn.), sodium larryl sulfate, magnesium lawyl sulfate, sodium oleate, sodium stearyl fumerate, DL-leucine, colloidal silica, and others as known in the art. Preferred lubricants are magnesium stearate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise 0.5 to 7.0% of the total tablet weight.

Other exciplents such as glidants and coloring agents may also be added to azithromycin tableta. Coloring agents may include thanium dioxide and/or dyes saitable for food such as those known as F. D. & C, dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, smato, carmine, turneric, peppita, and so forth. A coloring agent is an optional ingredient in the compositions of this invention, but when used will generally be present in an amount up to about 3.5 percent based on the total tablet weight.

As known in the art, tablet blends may be dry-granulated or wet granulated before tableting. Alternatively, tablet blends may be directly compressed. The choice of processing approach depends upon the properties of the drug and chosen excipients, for example particle size, blending compatibility, density and flowability. For azithromycin tablets, granulation is preferred, with wet granulation being most preferred. Azithromycin may be wet-granulated, and then other excipients may be added extragranularly. Alternatively, azithromycin and one or more excipients may be wet-granulated. In addition, tableta may also be coasted, with a coming that exhibits little or no effect on or interference with tablet dissolution, to assure case of awallowing or to provide an elegant appearance.

In a preferred embodiment, tablets of this invention are 63 film-coated to provide case of swallowing and an elegant appearance. Many polymeric film-coating materials are

8

known in the art. A preferred film-coating material is hydroxypropylmethylcellulose (HPMC). HPMC may be obtained commercially, for example from Colorcon Corp., in coating formulations containing excipients which serve as coating aids, under the registered trademark Opadry, Opadry formulations may contain factore, polydentrose, triacetin, polyethylsosgiycol, polyoorbate 80, titanium dioxide, and one or more dyes or lakes. Other suitable film-forming polymers also may be used horein, including, hydroxypropylcellulose, and acrylsto-methacrylate copolymers.

The tableting process itself is otherwise standard and readily practiced by forming a tablet from a desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press. Tablet formulation and conventional processing techniques have been widely described, for Example in Pharmaceutical Dosage Forms: Tablets; Edited By Lieberman, Lachman, and Schwartz; Published by Marcel Deidor, Inc., 2d Edition, Copyright 1989, the text of which is berein incorporated by reference.

The azithromycin dosage forms of this invention also include powders to make oral suspensions, and also the oral suspensions themselves. Generally the powder is a non-caking, free flowing powder which is sold direct to pharmacies or other retail outlets and then made up into the actual suspension by a pharmaciet. The oral suspension is thus the actual dosage form ingested by patients. The typical shalf life for a suspension is about five days because azithromycin therapy is generally of five days donation.

Azithromycin suspensions according to the invention contain, as necessary ingredients in addition to azithromycin, one or more thickening agents in a total amount of 0.1 to 2%, and a buffer or pH-altering agent in an amount of 0.1 to 2.5%, with percentages being based on the weight of the dry powder formulation. Dispersing agents may also be used in an amount of from 0.05 to 2%. Preservatives may also be used in an amount of from 0.11 to 2%.

Suitable thickening agents function as suspending agents and include, for example, hydrocolloid gums known for such purpose, examples of which include xanthan gum, guar gum, locust bean gum, gum tragacanth, and the like. Alternatively, synthetic suspending agents may be used such as sodium carboxymethylacthulose, polyvinylpymolidone, hydroxypropylechulose and the like.

Dispersing agents include colloidal allicon dioxide, available from Cabot Corporation, Boston, Mass. under the trade designation Cab-O-Sil.

For the purpose of preparing formulations of a powder for oral suspension, the bitter taste of azithromycin may be masked by including a basic buffer or pH-altering agent which will provide a pH of approximately 10 in the constituted suspension. Maintenance of the pH at around 10 minimizes the quantity of azithromycin in solution, and thus masks the bitter taste of the drug. Many combinations of flavors or flavor systems may be used in addition to mask the bitter taste of azithromycin. Preferred flavors are those which provide a constant flavor for approximately 5 days at the elevated pH of the formulation after constitution. A preferred flavor system consists of spray dried cherry #11929, artificial creme de vanilla #11489, and spray-dried artificial banana #15223 available commercially from Bush Booke Allen, Inc., Chicago, Ill. Artificial sweeteners may also be used.

A powder used to make a suspension herein may also contain conventional optional ingredients such as (1) westing agents such as sorbitan monolaurate, polysorbate 80, and sodium lawyl sulfate; (2) anti-fosming agents and (3) sweeteners and fillers such as glacose. The powder may also contain a buffer to maintain a high pH upon reconstitution, as discussed above. Suitable buffers and pH-altering agents

include anhydrous tribasic sodium photphate, anhydrous sodium earbonate, glycine, and the ilke. Suitable preservatives are well known, for example sodium benzoate and the like. After swallowing, azithromycin from a suspension dissolves quickly.

In the preparation of azithromycin powder for oral suspension formulations, all ingredients may be blended together and deagglomerated, as known in the art. Preferably, azithromycin and flavors are blended, and other ingredients are separately blended. Finally, these two blends are blended and deagglomerated.

Preferred oral suspensions are those which mauspend easily after constitution with aqueous media and which do not cake on storage after constitution. Preferred suspensions contain sucrose NF, when sucrose is used, and anhydrous excipients when available, to assure facile suspension upon 15 constitution. The drug-containing powder is generally reconstituted with water.

Suspensions of this invention exhibit about 90% dissolution of azithromycia in vitro in about 15 minutes. The test can be summarized as follows:

Shake the azithromycin-containing bottle to loosen the powder, and constitute the sample as per label instructions, e.g. as described in Example 12 to provide a 40 mg/ml azithromycin suspension. Shake the bottle vigorously for 2 minutes, then allow the bottle to sit for 30 minutes. Shake 23 again vigorously for 15 seconds. Withdraw 5 ml from the bottle (typically equivalent to 200 mg of azithromycin), taking care to eliminate air bubbles. Carefully dispense the 5 ml aliquot of the azithromycin suspension approximately 10 cm over the surface of the dissolution medium (0.10M 30 sodium phosphate buffer, pH 6.0) in a USP Appraxus 2, with the paddles positioned 2.5 cm from the bottom of the vessels. Begin rotating the paddles at 25 rpm, after the Oral Suspension samples have sunk to the bottom of the vessels. Remove approximately 10 ml from the dissolution vessel at each sampling time, filter, and assay filtrate for azithromycin using the HPLC assay described previously.

An azithromycin unit dose packet dosage form (also referred to herein as a "sachet") consists of a unit packet. designed to be emptied into an aqueous vehicle, for example water or a natural or artificial fruit heverage. The packet contains a blend of azithromycin and exciplents which is thus reconstituted. The packet contains, as necessary ingre-dients, azithromycin and a dispersing agent which makes the sachet powder free flowing, for example colloidal silicon dioxide such as Cab-O-Sil from Cabot, Generally the dispersing agent is present in an amount of about 0.2 to 2.0% by weight based on the weight of the dry suchet as it is to be sold. The dispersing agent also serves as a glidant. The formulation may also optionally contain ingredients including (1) a filler or swectener (e.g. glucose); (2) a buffer (e.g. 50 sodium phosphate); (3) a wetting agent such as a surfaceant, for example sodium lauryl sulfate, and (4) flavors such as any of those enumerated herein, and the like. The powder in the packet flows freely and disperses quickly, essentially immediately upon stirring when reconstituted. Azithromycin unit dose packet dosage forms may be prepared by blending and deagglomerating all ingredients, as known in the srt. and coaggromesing an ingrements, as anteres in the act.
Preferably, the filter (e.g. sucrose), buffer (e.g. subjectus
tribasic sodium phosphate), and glident (e.g. colloidal silicon dioxido) are blended and deagglomerated, followed by blending with azithromycin and flavore, followed by deagglomeration. The azithromycin in the packet dissolves quickly when evaluated as follows. The contents of a packet are added to a 250 ml beaker containing 60 ml water treated with the Milli-Q Plus system, Millipore Corp. (>18 mego-hms resistivity). The contents of the beaker are girred with a spoon until a homogeneous suspension is obtained (1-2 min.). With the paddles raised, the suspension is poused into

the center of a dissolution vessel of a USP-2 dissolution apparatus containing 900 ml 0.1M acdium phosphate buffer, pH 6.0. The paddles are then lowered into the vessel, and rotation is begin at 50 rpm. 10 ml. aliquots are removed at each time point, filtered, and filtrates are assayed for azithromycin in solution, using an HPLC assay as described above. Using this method, greater than 90% dissolution of a 1 gm azithromycin packet is observed in less than 5 minutes. The packet thus does not exhibit an adverse food effect.

10

As stated, the oral azithromycia dosage forms disclosed and described above can be administered to a mammal, including man, in need of such treatment when the mammal has exten, regardless of how recently and of the nature and pantity of food, without exhibiting an adverse food effect. To this end, and as an additional feature of the invention, this invention provides a therapeutic package suitable for com-mercial sale, comprising a container, an oral dosage form of arithromycin which does not exhibit an adverse food effect contained therein, and, associated with said package, written (i.e., printed) matter non-limited as to whether the dosage form can be taken with or without food. The written matter is of the type containing information and/or instructions for the physician, pharmacist or patient. The written material can be "non-limited as to whether the dosage form can be taken with or without food" by virtue of including no statement regarding whether or not the dosage form can be taken with or without food, i.e. the statement is silent with regard to food effects. Alternatively, the written material can be non-limited by containing one or more statements affir-matively informing the user (i.e., the patient, pharmacist, or manyley interming the user (i.e., the patient, pharmacist, or physician) that the said oral desige form can be taken by or administered to a patient regardless of whether the patient has exten or otherwise incided food (optionally, for example, also stating something like "without regard to type or quantity of food"). The written material can not contain ilmiting language with respect to food, e.g. This desage form can not be taken with food or This desage form may only be given after the patient has furted" or the like.

The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard hox, a glass or plastic bottle or jar, a re-sealable log (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual desages for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact desage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single desage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

Printed or otherwise written market is accordated with the

Printed or etherwise written matter is associated with the package in which the azithromycin dosage form is sold. The term "associated with" is intended to include all manners in which written matter, such as instructional or informational materials can be associated with a medicament, as known conventionally in the art. Thus written matter can be associated with the container, for example, by being: written on a label (e.g., the prescription label or a separate label) adhesively affixed to a bottle containing an azithromycin suspension; included inside a container as a written package insort, such as inside a box which contains unit dose packets; applied directly to the container such as being printed on the wall of a box; or anached as by being tised or taped, for example as an instructional card affixed to the neck of a bottle via a string, cord or other line, lanyard or tether type device. The written matter may be printed directly on a unit dose pack or blister pack or blister card. If the written matter affirmatively contains a non-limiting statement, the written matter

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11

matter may contain other information in addition. An aftirmative non-limiting statement may, for example, read like the following exemplary statement:

This product does not exhibit an adverse food effect and may accordingly be administered to patients whether or not they have eaten and without regard to type or quantity of food.

or something similar, such as "may be taken without regard

The invention will now be illustrated by the following examples which are not to be taken as limiting. In general, the examples demonstrate that (1) azithromycin capsules exhibit an adverse food effect, and that more slowly dissolving capsules exhibit a larger food effect, and (2) arithmycin fast dismiving tables, powder for oral suspension, and unit dose packet dosage forms do not exhibit an adverse food 15

EXAMPLE 1

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of arithromycin 20 dosed in a capsule dosage form with moderate dissolution

Capsules were prepared which contained 250 mg activity azithromycin. The formula for these capsules is pres Table 1. The dissolution behavior of these capsules was 25 evaluated by the method previously discussed, using rotat-ing paddles, 100 rpm, 900 ml pH 6.0 phosphate buffer at 37 degrees C. The average % azithromycin dissolved at 15 minutes was 25%, and at 30 minutes was 76%.

The effect of feeding on szithromycin blosvallshility was 30 determined as follows. Eleven healthy male human volunteers were orally dosed with 500 mg azithromycin (2c250 mg capsules), on each of 2 occasions. On one occasion, the ing Capanics), on each to a because the state food and fluid) subjects were dosed after an overnight fast (food and fluid) of 12 hr. The dose was swallowed with 150 ml water, and a further 150 ml water was taken at I hr post-dosing. On the other occasion, the subjects consumed a meal consisting of milk, bread and butter, bacon, 2 fried eggs, and coffee. The dose was administered with 150 ml water within 30 minutes of completion of the meal. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr 40 post-dosing. Serum arithmomycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the an under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition. The ratio 45 was constrained for each receipt constron. In: many AUCfad/AUCfasted was used as a measure of the effect of food on oral bloavailability. The average AUCfad/AUCfasted was 0.22, with lower and upper 90% confidence levels of 0.06 and 0.84, respectively.

TABLE I

*Based on a bulk potency of 94.8%; Non-tolchicamenic hydrae.

EXAMPLE 2

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin

65

dosed in a capsule dosage form which dissolved more quickly than the cansules of Haample 1.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycln from these capsules was evaluated as in Example 1. In 15 minutes, 97% of the encapsulated azithromycin was

The effect of feeding on azithromycin bioavallability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg szithromycin (2:250 mg capsules), on each of 2 occasions.
On one occasion, the subjects were doed after an oversight fast, and on the other occasion the subjects were doed after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two ounces of ham, two pieces of toast with two teappoins of latter and two pats of jelly, and eight ounces whole-fat milk. The oral doses were administered with 250 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-doeing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on azithromycin oral bioavailability. The average AUCfed/AUCfasted was 0.80, with lower and upper 90% confidence levels of 0.67 and 0.96, respectively.

TABLE II

Formula for Authorosycia capualus. This formula was prepared a a dry generation and was loaded into 60 opeque locking capualus.				
INGREDIENT	MG/CAPSULE			
Azidromycia Dibydrac*	262.05			
Lactors, anhydrous	151.55			
Corn starch, hydrous	47.00			
Magmatium steerste/Sodiess Jeuryl sulfate	9.40			
TOTAL				

*Equivalent to 250 mg anithmosycla, bused on a bulk potency of 95.4%.

EXAMPLE 1

This example is comparative and demonstrates the effect of a light breakfast on systemic exposure of azithromycin dosed in a capsule dosage form which dissolves quickly,

Azithromycin capsules (250 mg attength) were prepared according to the formula in Table II. Dissolution of sziknomycin from these capsules was evaluated as in Rusmple 1. In 15 minutes, 99% of the encapsulated azithromycin was

The effect of a light (Continental) breakfast on azithro-mycin bioavailability from this dosage form was determined as follows. Twelve healthy male larman volunteers were orally doted with 1000 mg azithromycin (4x250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 br fast, and on the other occasion the were dosed after a 12 hr fast, and on the other occasion the subjects were dosed after consumption of a light breakfast consisting of two rolls with butter and jam and Ca. 300 ml of coffee or tes with milk. The oral doses were administered with 240 nal water. Blood samples were withdrawn prior in dosing, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 46.5 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the

area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfested was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.71, with lower and upper 90% 5 confidence levels of 0.53 and 0.95, respectively.

EXAMPLE 4

This example demonstrates the effect of a high fat break- 10 fast on systemic exposure of azithromycia dosed in a tablet dosage form which dissolves quickly.

Azithromycin tablets were prepared according to the formula given in Table III. Dissolution evaluation was carried out as in Example 1. At 30 minutes, 100% of the 15 azithromycin was dissolved.

The effect of feeding on azithromycin biografiability from these tablets was determined as follows. Twelve healthy male human wolumeers were erally dosed with 500 mg azithromycin (25/250 mg tablets), on each of 2 occasions. On 20 one occasion, the subjects were dosed after an overnight fant, and on the other occasion the subjects were doted after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of becon, two pieces of loss: with two teaspoons of butter and two pats of jelly, eight cunces whole-fut milk, and 6 cunces hash-knows possess, ingested over a twenty minute period. The oral doses were administered with 240 ml water. Blood samples were with cleawn prior to dozing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 in post-dosing. Serum szithromycia concen-tration was determined using a high performance liquid 30 chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condi-

The ratio AUCfed/AUCfasted was used as a measure of 35 the effect of food on oral bioavailability. The average AUC/feet/AUC/seted was 0.97, with lower and upper 90% confidence levels of 0.82 and 1.13, respectively.

TABLE III

Formula for arithrowycia film count tablets. This formula was compressed to form a 0.262° × 0.5312° modified capsular, upper captured "Pfater", lower accord, tablet, and was counted with "pfate Opachy".

INGREDIENT	WEIGHT (MO/UNIT)
Asidronycis dilrydrae*	262.05
Pregalateland starch**	27.00
Calcless phosphete dibasic, ankydrous Sodiera erosematikus ^{a w}	138.84
Magnesium statemie/Sodium japryl	9.00
acifes (90/10)	13.[1
Mak Opedry Heir	18.00

^{*}Repivalent to 250 mg arithmosycia, based on a bulk potency of \$5,4%, Ac-Di-Sol

EXAMPLE 5

This example demonstrates the effect of a Ispanese meal on systemic exposure of azithromycin dosed in a tablet doesge form which dissolves quickly.

A tablet desage form of szithrossycia was prepared according to the formula described in Table IV. Dissolution 65 of this desage form was evaluated as in Example 1. In 15 minutes, 100% of the azithromycin dose was dissolved.

14

The effect of feeding on azithromycin bioavailability from these tablets was determined as follows. Eight healthy male human volunteers were orally dosed with 500 mg azithromycla (2x250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed 30 minutes after the other occasion the subjects were to see 30 numbers area consumption of a Japanese meal consisting of rice, miso soup, fried egg, seaweed, spinsch, and pickles. The oral doses were administered with 200 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug acrum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.00, with lower and upper 90% confidence levels of 0.87 and 1.15, respectively.

TABLE IV

Andercoycle film-count tablet formule. Captalar plain white firm-control tablets (0.262" x 0.5312") were compressed and then counted with "White Opedry" and "Clear Opedry".

WEIGHT (MG/TABLET)
262.05
27.00
138.34
9.00
J2325
0.675
13.11

*Bourvalent to 230 mg exhikmenycia, based on a balk poiceary of 95.4%. **Smerth 1900. ***Ac-Di-Sol.

Paramonia. Comains phydroxymogyd enstkylcellulose, blumiam dioxide, polyethylcang-ol, and polyecybaie 80, Comains hydroxymogyl methylcellulose and polyedylaneglycol.

EXAMPLE 6

This example compares the effects of a high fat breakfast and a low fat breakfast on systemic exposure of azithromycin doeed in a "Powder for Oral Suspension" doeage form.

An azithromycin "Powder for Oral Suspension" was perpered according to the formula in Table V. This formula was designed to wet and disperse quickly when reconstituted with an aqueous vehicle. Dissolution of this ampenaton was evaluated as described in the "Detailed Description". In 15 minutes 97% of the azithromycin dose dissolved; in 30 minutes 99.6% of the azithromycin dose dissolved.

The effect of a high fat meal and a low fat meal on azithromycin bioavailability from this suspension dosage form was determined as follows. Six healthy male human form was getermined as roucows. Six seariny made number welconterns were orally dosed with 500 mg arithromycin (12.5 m) of a 40 mg/ml onal suspension), on each of 3 occasions. On one occasion, the subjects were dosed after an overright fast of 10–12 in. On another occasion the subjects were dosed after consumption of a high fat meal consisting of the same field in one tablement better two series of of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two pats of butter, eight courses whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. On the third occasion, the subjects were dosed after consumption of a low fat meal consisting of one cunce of Checrics (registered trademark of

⁶⁰ Contains introse, hydrosypropyl methylcellulose, titarium dioxide, tri tin, and D&C Red No. 30 Alexanaeca Lain.

15

General Mills Inc.) cereal and eight ounces of whole milk. The oral doses were administered with 240 ml water (two 60 mi rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 br post-dosing. Sexum szithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dusing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. For the high fat meal, the average AUCfed/AUCfasted was 1.01, with lower and upper 90% confidence levels of 0.79 and 1.28, respectively. For the low fat meal, the average AUCred/AUCrested was 1.04, with lower and upper 90% confidence levels of 0.82 and 1.33, respectively.

TABLE V

arder for Oral Supposed on

Personale for anithmentor "To

To reconstitute this farmulation, 0.52 ml water was added per gm. dry formulation.		
INGLEDIENT	WEIGHT (MC/BOTTLE)	
Azideousycio dihydrate* Sucrese Sodiem phosphate tribusic,	838.57 15487.74 70.01	_ 2
anhydraus Hydrauspropyleithdese (Klucel- EP)	26.62	
Finance gara (Kelbol) FDAC Red #40 Spany Dried Cherry #11929	26,62 0.67 59,54	3
Art. Creme do Vanille #11489 S.D. Art. Bangue #15223	131.28 99.96	•
TOTAL	16743,41	

⁴Bated on a bulk potency of 95.4%.

EXAMPLE 7

This example demonstrates the effect of a high fat break- 40 fast on systemic exposure of azithromycin dosed in a "Single Dose Packet" (sachet) dosage form.

A "Single Dose Packet" (sachet) dosage form of azithromycin was prepared according to the formula described in Table VI. Dissolution of this desage form was evaluated as 45 described in the "Detailed Description" above. In 15 minutes, 99% of the azithromycia was dissolved.

The effect of feeding on azithromycin bioavallability from this sachet dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (1 gm sachet), on each of 2 occasions. On

16

one occasion, the subjects were dosed after an overnight (ast of at least 12 hr, and on the other occasion the subjects were dosed after consumption of a high-fat meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two places of toast with two teaspoons of butter and with two pats of Jelly, eight ounces whole fat milk, and 6 ounces hash-brown potatoes. The oral doses were administered with 240 ml water (two 60 ml rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to doeing, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, and 120 br post-dosing. Serum azithromycin concentration was determined using a high performance. liquid chromstography array. For each subject under each dowing condition, the area under the drug serum concentra-tion vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavaliability. The average AUCfed/AUCfasted was 1.12, with lower and upper 90% confidence levels of 0.99 and 1.27.

TABLE VI

concle for mishonespein "Unit Done Pacies" donage form, This blend was proposed, and filled into 3.25 × 4" white paper altersistant/polyethylens intoinste melets. To reconstitute for doning, the contents of a melet is added to 50 ml water, and

INCHEDIENT	WEIGHT (GM/LINIT)
Anithmaycin dikydoge*	1.048
Socrose	9.707
Sodiam phosphate tribusic, ashydrous	0.062
Colleidel silicon dieside	0.055
Spray Deird art. charry #11929	0.038
Spray Dried ers. beneza #15223	0.064
TOTAL	11,000

^{*}Equivalent to 1 gas michromycis, based on a bolk potency of 95.4% for michromycis dilaydrate.

RYAMPI F 8

Azithromycin tablets of this invention were prepared at 150, 200, 250, 300, 500, and 600 mg dosage strengths. Third cores were prepared by wet granulation of all inhiest core ingredients (except magnesium steamte/sodium lany) sulfate). The dried granules were blended with the lubricant mixture magnesium stearste/sodium lauryl sulfate, followed by tableting on a tablet press. Tablets were conted with an aqueous film cost comprising colored and/or clear Opadry. These tablet formulations do not exhibit an adverse food effect. Tablet formulations were as described in Table VII.

TABLE VII

Rustopics of existenceycin tablet formulations which do not exhibit a food effect.						
WEIGHT (MG/TARLET)						
Сострония	150 MG STRENGTH	200 MG STRENGTH	250 MO STRENGTH	300 M/J STRENUTH	500 MO STRENGTH	600 MG STRENOTH
Azithromycia dibydrata*	157.23	209.513	267.05	314.44	574.10	624.93
Progolaticisod starch**	16.20	21.50	27.00	32.40	54.00	64.80
Culcium phosphate diberic, antrydross	23.305	111.01	138.64	166.61	277.68	333.22
Sodium eroscume)- Josef	5.400	7.200	9.00	10.80	18.00	21.60

17

TABLE VII-continued						
_	Buscuples of szithr	omycio tablet for	mulaciona which	do not entribit a	Good effect.	· · · · · · · · · · · · · · · · · · ·
Сотронен	WEIGHT (MG/TABLET)					
	150 MG STRENGTH	200 MG STRENOTH	250 MG Strength	300 MG STRENGTH	990 MO STRENOTH	600 MG STRENGTH
Magacaium steamha/ Sodiam lamyl miliste (90/10)	7.865	10.495	13.11	15,73	26.22	31.46
Opedry @	<u> 1.1 </u>	10.8	13.5	16.2	27.0	32.4
TOTAL	278.1	370.8	463.5	556.2	927.0	1,112.4

TABLE IIII annihmad

EXAMPLE 9

Additional tablet formulations of azithromycin (250 mg) are prepared which do not exhibit an adverse food effect and are described in Table VIII. The diluent in these formulations (calcium phosphate dibasic, subydrous) may be substituted by calcium phosphate dibasic dihydrate, microcrys- 25 talline cellulose, lactoso NF/BP/EP/IP, or other appropriate diluent. The lubricant in these tablets (magnesium steamer sodium lauryl sulfate, 90/10) may be submituted by magnesium stearate and/or colloidal allica or acdium atearyl furnarate. Magnesium stearate and sodium stearyl furnarate 30 are generally used in amounts constituting 0.5-7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1-1% of the total tablet weight. While considerable latitude in relative excipient ratios is possible, 35 the calcium phosphate/pregelatinized starch ratio should be around 2:1 or greater. The Opadry film cost is not necessary to achieve food-independent drug exposure, but serves to improve ease-of-swallowing and tablet appearance and serves to differentiate strengths. The Opadry cost may 40 comprise between 2-6% of the total tablet weight. Tablets at other potencies may be obtained by maintaining the approxi-mate azithromycin/exciplent ratios described in Table VIII, and increasing or decreasing total tablet weight.

TABLE VIII Examples of sections system tables formulations (250 mg) which do not exhibit as adverse fixed effect.

	WEIGHT (MG/TABLET)				
COMPONENT	FORMU- LATION 1	PORMU- LATION 2	PORMU- LATION 3	- 3	
Azidaranycio d'Orydone	262.05	262.05	262.05	•	
Progeletinized starch	50.0	13.9	\$0.0	5	
Calcium phosphete dibasic, sub.	11784	140.94	104.84		
Sodiam concentration	9,0	30.0	20.0		
Magazziner Zimuniologiani	13.11	13.11	13.11	4	
lauryi selfate Opadry ii	13.50	13.50	13,50		
TOTAL	463.5	463.5	463.5		

naypropylmothylasthalose and appropriate pleaticiners, film-centing its reactions, and labor.

EXAMPLE 10

18

Further 250 mg azithromycin tablet formulations are prepared which do not exhibit an adverse food effect and are presented in Tables IX and X. In these formulations, maize starch, sodium starch glycolate, and crosslinked polyvinyipyrrolidone serve as disintegrants. Calcium phosphate dibasic, lactose NF/BP/RP, and microcrystalline cellulose scree as diluents.

Magnesium stearate/sodium lauryl sulfate serves as a lubricant. Magnesium sterrate/sodium lauryl sulfate may be substinted by magnesium stearate and/or colloidal silica or sodium steary! fumerate. Magnesium stearate and sodium steary! fumerate are generally used in armounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1–1% of the total tablet weight. While considerable lailtude in relative encipient ratios is possible, the diluent/disintegrant ratio should be around 2.1 or greater. The Opadry film cost is not necessary to achieve food-independent drug exposure, but serves to improve case-of-swallowing and tablet appearance. The Opadry cost may comprise between 2–6% of the total tablet weight. Tablets at other potencies are obtained by maintaining the approximate azithromycin/excipient ratios described in Tables IX and X, and increasing or decreasing total tablet weight. These formulas are illustrative, and substitutions of other disintegrants, diluents, and lubricants are possible, as substituted by magnesium stearate and/or colloidal silies or other disintegrants, diluents, and lubricants are possible, as 45 known in the art.

TABLE IX

	ist formulation wi find offe	ich do na eniji a.	i as adverse
	WEIGHT (MG/TABLET)		
COMPONENT	PORMU- LATION 4	FORMU- LATION 5	PORMU- LATION 6
Azithronycia Okydunt	262.05	262.05	262.05
Maine starch* Calcism phosphate, dibasic** OR	11.9 151. 34	27.0 13 4.8 4	59.0 115.84
Lactore NF/MPEP/IP OR Microcrystalline collaions			
Section starch glycologii OR Crossielad polyrisylpycroli-	9 0	9.0	9.0

tency of \$5.4%.

^{**}Starch 1500.

SIE ADDISO

[@]Hydroxypropylecethylecthulour and appropriate planticisms, film-coating adjuvents, opacifier, and lakes.

19

TABLE IX-continued

azithremycia tablet formulations which do not exhibit an adverse food effect.				
	WEIGHT (MOTABLET)			- 5
COMPONENT	PORMU- LATION 4	PORMU- LATION 5	PORMU- LATION 6	
Magnesiasa stematokodises lasnyi saifate	13.11	13.11	13.11	- 10
Opadry 4	13.5	13.5	13.5	
TOTAL.	463.5	463.5	463 <u>.</u> 1	
Equivalent to 250 p	e midromycia.			. 15

*Also called starch NF or corrected.

**Riber extractions or disydram

#c.g. Explain or Principal

#d.g. PVP-XL from International Sp

Examples of arities

ani Specially Products Inc

OHydroxympytractrylacilolose and appropriate planticiners, file-contents
adjovants, opecifics, and lakes.

TABLE X

m náverné food effect.

nych tablet formulations which do not exhibit

13.5

463.5

13.5

463.5

				-
	WEIGHT (MG/TABLET)			_
COMPONENT	FORMU- LATION 7	PORMU- LATION &	FORMU- LATION 9	
Asideranycia Albertanici	262.05	262.05	262.05	_ 3
Malan stands Chicken phosphate, dhosic** OR Lacton	13.9 140.94	27.0 144.24	27.0 127. 34	
NP/BP/RPUP OR Microrrystalline cultaines Sodium starch glycelated OR Crossibles	20.0	3,0	20.0	3
polyvinylyymii- donelli Magazzium Magazzium	13.11	13.11	13.11	

"Also called storch NF or constants

بمكند ارسا

TOTAL

"Also culied starch NF or communes
"Either subjectes or diltydrate
for, Esplone or Principal
for, Esplone or Principal
files, PriP-XL from humaniousi Specialty Products for,
@Hydensymographysochilose and appropriate planticis
adjovenite, specificre, and lates.
TEquivalent to 250 mg midwomycin.

13.5

463.5

EXAMPLE 11

The "Powder for Oral Suspension" formulation described in Table XI was prepared. This formulation does not exhibit 60 an adverse food effect.

TABLE XI

20

der for Oral Suspension*
WEIGHT (MOVOM)
47.97
579.71
289.86
18.84
4.35
14.49
14.49
1.45
5.80
15.26
7.63
0.15
1000.00

EXAMPLE 12

Azithromycin "Powder for Oral Suspension" formulations are prepared as illustrated in Tables XII and XIII. The
unit potency of these formulations is 600 mg szithromycin/
bottle, and the use potency after constitution with water is 40
mg/ml. To constitute, 0.52 ml water is added per gm of
blend. 9 ml. water and 16.74 gm blend produce approximately 20 ml suspension. These formulations include 200
mg Azithromycin/tottle overfill. The listed "flavor system"
may be freely substituted with other flavors which provide
a pleasant taste and are stable at pH 10 over the shelf-life of
the constituted suspension (approximately 5 days). The dye a pressure takes and are alone at per 10 over me seek-life or the constituted suspension (approximately 5 days). The dye may also be freely substituted. The formulations in this Example are illustrative, and not limiting. These formula-tions do not exhibit an adverse food effect.

TABLE XII

		Supersi	xe*	······
40	•	WEIGHT OMG/BOTTLE		
	COMPONENT	FORMU- LATION 1	PORMU- LATION 2	PORMU- LATION 3
45	Anithronycia Glydesia	234.5 7	£31_57	83 2. 57
73	Secres NF	15487.74	15370.54	15487.74
-	Sodiem phospinae Missio anbydrios	70.01	70.01	70,01
	H ydroxypropy). callulose	26.62	24.62	0
50	Xeeber gen	26.62	26,62	0
	methyleciluless	0	0	53.24
	Colloidai siiteen dieside	O	16.74	0
	Olyclas	0	100.46	٥
55		\$9.94	59.94	59.94
	Art. Crosse de Vanilla #11489	133.28	133,28	133.28
	Spany-dried Art. Researce 015223	99.96	99.96	99,96
60	FD&C Red #40	0.67	0.67	0.67
_	TOTAL.	16743.41	16743.41	16743.41

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20

21

TABLE XIII

22	
TABLE :	۲V

Examples of formulations of Azidromycia "Foreier for Oral Suspension"				
	WEIGHT (MO/BOTTLE			
COMPONENT	FORMU- LATION 4	PORMU- LATION 5	PORMU- LATION 6	
Asidatomycia diliydraic	E38.57	£3£.57	838.57	
Scrittol	15138.55	7743.87	2656.37	
Socress NF	0	7743.87	7656.37	
Sodism curbonas, aniquirus, NF	302.00	0	150.00	
Sodium phosphus tribule autydrau	0	70.01	35.00	
Hydroxypropyl- cellulose	0	26.62	17.75	
Xandani gara	٥	26.62	17.75	
Sodium carboxy- metrylexitatose	53.24	9	17.75	
Colloidej sticos dioxide	16.74	0	10.00	
Glycine	100.46	٥	50.00	
Spury-dried charry #11929	59.94	39.94	59.94	
Art. Crease de Vanitia 811489	133.28	133.28	133.20	
Spray-deind Act. Beauting #15223	99.96	99.96	99.96	
FD&C Red #40	067_	0.67	<u> </u>	
TOTAL.	16743.41	16743.41	16743.41	

EXAMPLE 14

The following formulations of unit dose packets of 35 azithromycin are prepared as being exemplary, not limiting, of the invention (Tables XIV and XV). The flavor system for these dosage forms may be freely substituted with any flavor system which provides a pleasant taste when the contents of 40 the packet are reconstituted in water or an aqueous beverage. When constituted in water or an aqueous beverage, these dosage forms do not exhibit an adverse food effect.

TABLE XIV

Examples of suit dose packet forestations.				
COMPOSITION	POSUMU- LATION I	PORMU- LATION 2	PORMU- LATION 3	
Anishromycia diliyeran	1.048	1.048	1.048	
	9.707	9.707	5.0	
embicol	0	0	G	
accinen	0.04	0.2	0.062	
phosphate tribuic, anhydrous				
nodium carbonate, entration	0	0	0	
glycles	0		o	
colloidal alticon dioxida	0.022	0.22	5.053	
Spony-dried art. cherry #11929	0.034	0.038	0.038	
Spray-dried are.	0.064	0.064	0.064	
P15223				

	plet of sait does p	THE PERSON	<u>-</u>
COMPOSITION	PORMU- LATION 1	FORMU- LATION 2	PORMU- LATION 3
Azithratoycia dibydrate	1.048	1.048	1,048
microno acublici sodiom phesphate	0 9.707 Q.068	4.85 4.85 0.088	4.85 0.044
tribasic, mäydrosa Jodiem Carbonaic, ashydrosa	a	0	0.022
glycine colloidal silicon dicoide	0 0.055	0 0.055	0.022 0.055
Spray-dried art. charry #11929	0.032	6.034	0.034
Spray-dried art. HISO23	0.064	0.064	0.064

What is claimed in:

- 1. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is aiministrable to a mammal that has eaten, which comprises azithromycin and a disintegram, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the desage form equivalent to 200 mg of azithromycin is tested as set forth in USP test </11> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less then a taste-masking amount of an alkaline earth metal oxide or hydroxide.
- 2. A dosage form as defined in claim 1, wherein said mammal is a human
- 3. A dosage form as defined in claim 1, further comprising
- a flavoring agent.

 4. An oral dosage form of szithromycin which is in the form of a powder for oral suspension containing anhydrous buffer, which is administrable to a mammal that has exten, which comprises azithromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of arithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a teste-masking 55 amount of an alkaline earth metal oxide or hydroxide.
 - 5. A douge form as defined in claim 4, wherein said mammal is a human.
 - 6. A douge form as defined in claim 4, further comprising a flavoring agent.
 - 7. A dosage form as defined in claim 6, wherein said flavoring agent is a flavor system consisting of cherry, vanilla, and banana.
 - 2. A dosage form as defined in claim 4, in the form of a suspension made from said powder.
 - 9. An oral dosage form of azithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has caten, which

comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dougge form effecting at least about 90% dissolution of azithromyclo within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <7i1> in a USP-2 dissolution apparatus unde in USF test CALP in a USF-2 unnumber appearance standard conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said desage form contains least than a teste-masking amount of an alkaline earth metal oxide or hydroxide.

18. A dosage form as defined in claim 9, wherein said manimal is a human.

11. A dotage form as defined in claim 9, further comprising an anhydrous builler.

12. A dosage form as defined in claim 9, wherein said 15 dispersing agent is colloidal allicon dioxide.

13. A dosage form as defined in claim 9, in the form of a

- suspension made from said unit dose packet.

 14. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is admin- 20 istrable to a mammal that has esten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form exhibiting a value of (AUC_{pac})(AUC_{pac}) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said desage form 25 contains less than a teste-masking amount of an alkaline earth metal oxide or hydroxide.
- 15. A dosage form as defined in claim 14, wherein said manunal is a human.

16. A douge form as defined in claim 14, further com- 30 prising a flavoring agent.

- 17. An oral desage form of azithromycin which is in the form of a powder for oral suspension containing an anhydrous buffer, which is administrable to a mammal that has eaten, which comprises azithromycin, one or more thicken- 35 ing agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form exhibiting a value of (AUC, /(AUC,) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a trute-masking amount of an aikaline 40 earth metal oxide or hydroxide
- 18. A dosage form as defined in claim 17, wherein said mammal is a human.
- 19. A dosage form as defined in claim 17, further comprising a flavoring agent.
- 20. A dosage form as defined in claim 19, wherein said flavoring agent is a flavoring system consisting of cherry, vanilla, and banana.

21. A dosage form as defined in claim 17, in the form of a suspension made from said powder.

22. An oral desage form of szithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has caten, which comprises azithromycin and said dispersing agent, and comprises extensionycon and sum cospersing agent, and which exhibits no adverse food effect, said dosage form 55 exhibiting a value of (AUC_{ped})/(AUC_{ped}) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

23. A dosage form as defined in claim 22, wherein said 60 mammal is a hungo.

24. A dosage form as defined in claim 22, further comprising an anhydrous buffer.

25. A dosage form as defined in claim 22, wherein said dispersing agent is colloidal silleon dioxide.

26. A douge form as defined in claim 22, in the form of a suspension made from said unit dose packet.

27. A dosage form as defined in claim 1, comprising: 58.2% azithromycin dihydrate;

6.0% pregelatinized starch;

30.9% anhydrous dibasic calcium phosphate;

2.0% sodium croscarmellose; and

2.9% Jubricant.

28. A dosage form as defined in claim 1, comprising: 58.2% azithromycin dibydrate;

11.1% progriatinized starch;

25.7% anhydrous dibasic calcium phosphate;

2.0% sedium croscarmellose; and

2.9% lubricant.

29. A dosage form as defined in claim 1, comprising:

58.2% azithromycin dihydrate;

3.1% pregelatinized starch;

31.3% anhydrous dibusic calcium phosphate:

4.4% sodium croscarmellose; and

2.9% lubricant

30. A dosage form as defined in claim 1, comprising:

58.2% azithromycin dihydrate;

11.1% pregalatinized starch;

23.3% anhydrous dibasic calcium phosphate;

4.4% sodium croscarmellose; and

29% lubricant

31. A dotage form as defined in claim 1, comprising:

58.2% azithromycin dihydrate;

3.1% maize starch;

33.8% dibasic calcium phosphate, lactore, or microcrystalline cellulose:

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricum.

32. A dosage form as defined in claim 1, comprising:

58.2% azithromycin dihydrate:

6.0% make starch;

30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose:

2.0% sodium starch glycolate or crosslinked polyvinylpymolidone; and

2.9% lubricant.

33. A dosage form as defined in claim 1, comprising:

58.2% azithromych dibydrate;

11.1% maize starch;

25.7% dibasic calcium phosphite, lactose, or microcrystalline cellulose;

2.0% actium starch glycolate or crosslinked polyvinylpymolidone; and

2.9% Jubricant

34. A dosage form as defined in claim 1, comprising:

58.2% azlıbromycin dibydrate;

3.1% main starch;

31.3% dibiaic calcium phosphate, lactose, or microcrystalline cellulose;

4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% Jubelcant

35. A dosage form as defined in claim 1, comprising:

58.2% azithromycin dibydrate;

6.0% malac starch;

26 32.2% dibatic calcium phosphate, lactore, or microcrys-42. A dosage form as defined in claim 4, comprising: tallino cellulose: 5.0% azithromycin dihydrate; 0.7% sodium starch glycolate or crosslinked polyvi-46.3% sorbitol: nylovnolidone: and 46.3% sucrose: 2.9% lebricant. 0.4% anhydrous tribasic sodium phosphate; 36. A dosage form as defined in claim I, comprising: 0.2% bydroxypropylmethylocilulose; 58.2% azithromycia dihydrate: 0.2% xanthan gum; and 6.0% maize starch; trace coloring 28.4% dibasic calcium phosphate, lactose, or microcrys-1.8% flavoring. talline cellulose; 43. A dosage form as defined in claim 4, comprising: 4.4% sodium starch glycolate or crosslinked polyvi-5.0% azlihromych dihydrate; nylpyrrolidone; and 45.7% pucrose: 29% labricant 45.7% sorbital: 37. A dosage form as defined in claim 4, comprising: 15 0.9% anhydrous sodium carbonate: 5.0% azithromycin dihydrate; 0.2% anhydrous tribasic sodium phosphate; 92.5% sucrose; 0.1% hydroxypropylmethylcallulose; 0.4% anhydrous tribasic sodium phosphate; 0.1% zaothm gum; 0.2% hydroxypropylecilulose; 0.1% sodium carboxymethylcellulose: 0.2% xaothan gum: C.1% colioidal allicon dioxide; trace coloring; and 0.3% glycine; 1.8% flavoring. trace coloring; and 38. A dosage form as defined in claim 4, comprising: 1.8% flavoring. 4.8% azithromycin dihydrate; 44. A douge form as defined in claim 9, comprising: 58.0% sucrose; 9.5% azithromycin dibydrate; 29.0% sorbital: 88.2% sucrose; 1.9% anhydrous sodium carbonate; 0.8% anhydrous tribusic sodium phosphate; 0.4% sodium benzoate; 0.5% colloidal silicon dioxide; and 1.5% tragacanth gum powder; 0.9% flavoring. 1.5% titanium dioxide; 45. A dosage form as defined in claim 9, comprising: 1.15% colloidal silicon dioxide; 9.5% azlibromycia dibydrate; 0.6% glycine; and 88.2% sorbitol; 2.3% Revoring. 0.8% anhydrous tribasic sodium phosphate; 39. A dosage form as defined in claim 4, comprising: 0.5% colloidal nilicon dioxide; and 5.0% azithromycin dihydrate; 0.9% flavoring. 91.8% sucrose; 45. A doarge form as defined in claim 9, comprising: 0.4% anhydrous tribasic sodium phosphate; 9.6% azithromycin dihydrate; 0.2% hydroxypropylcellulose; 88.9% gucrose: 0.2% xanthan gum; 0.4% anhydrous tribunic sodium phosphate: 0.1% colloidal silicon dioxide; 0.2% colloidal silicon dioxide; and 0.6% glycine; 0.9% flavoring. trace coloring; and 47. A dosage form as defined in claim 9, comprising: 1.8% flavoring. 9.3% azithromycin dibydrate; 40. A douge form as defined in claim 4, comprising: 86.1% sucrose: 5.0% szithromycin dihydrate; 1.8% anhydrous tribasic sodium phosphate; 92.5% sucrose: 2.0% colloidal silicon dioxide; and 0.4% unhydrous tribasic sodium phosphate; 0.9% flavoring. 0.3% sodium carboxymethylocllulose; 48. A dosage form as defined in claim 9, comprising: trace coloring; and 16.7% azithromycin dihydrate: 1.8% flavoring. 79.5% sucrose: 41. A dosage form as defined in claim 4, comprising: 1.4% anhydrous tribesic sodium phosphate; 5.0% azithromycin dihydrate; 0.9% colloidal allicon dioxide; and 90.4% sorbitol: 1.6% flavoring. 1.8% anhydrous sodium carbonate: 49. A dosage form as defined in claim 9, comprising: 0.3% sodium carboxymethylcellulose; 9.5% azithromycio dibydrate; 0.1% colloidal silicon dioxide; 44.1% sucrosc: 0.6% glycine; 44.1% sorbital: trace coloring; and 0.8% anhydrous tribusic sodium phosphate; 1.8% flavoring. 0.5% colloidal allicon dioxide; and

27 0.9% flavoring. 58.2% azithromycin dihydrate; 50. A dosage form as defined in claim 9, comprising: 3.1% maize starch; 9.5% azithromycin dihydrate; 31.3% dibasic calcium phosphate, lactose, or microcrys-44.1% sucross: talline cellulose: 44.1% sorbitol; 4.4% sodium starch glycolate or crosslinked polyvi-0.4% anhydrous tribasic sodium phosphate: nylpyrrolldone; and 0.2% anhydrous sodium carbonate; 2.9% lubricant 0.2% glycine; 59. A dosage form as defined in claim 14, comprising: 0.5% colloids silicon dioxide; and 58.2% azithromycin dihydrate: 0.9% flavoring. 6.0% makes starch; 51. A dosage form as defined in claim 14, comprising: 32.2% dibasic calcium phosphate, lactose, or microcrys-58.2% azithromycin dibydrate; talline cellulose: 6.0% pregulatinized starch: 0.7% sodium starch glycolate or crosslinked polyvi-30.9% anhydrous dibasic calcium phosphate; nylpymolidose; and 2.0% sodium croscomellose; and 2.9% lubricant 2.9% lubricant. 60. A dosage form as defined in claim 14, comprising: 52. A dosage form as defined in claim 14, comprising: 58,2% azithromycio dihydrate; 58.2% szitkromycia dihydrate; 6.0% make starch: 11.1% progelatinized starch: 28.4% dibusic calcium phosphate, lactore, or microcrys-25.7% anhydrous dibasic calcium phosphate; talling callulose: 2.0% sodium croscermeilose; and 4.4% sodium starch glycolate or crosslinked polyvi-2.9% lubricant. nylpymolidone; and 25 53. A dosage form as defined in claim 14, comprising: 2.9% hibricant A dosage form as defined in claim 17, comprising: 58.2% azlibromycin dihydrate: 3.1% pregelatinized starch; 5.0% azithromycin dibydrate; 31.3% anhydrous dibasic calcium phosphate; 92.5% sucrose: 4.4% sodium croscarmellose; and 0.4% anhydrous tribasic sodium phosphate; 2.9% lubricunt 0.2% hydroxypropylecilulose; 54. A dosage form as defined in claim 14, comprising: 0.2% xanthan gum; 58.2% azithromycin dibydrate; trace coloring; and 11.1% pregolatinized starch; 1.8% flavoring. 23.3% anhydrous dibasic calcium phosphate; 62. A dosage form as defined in claim 17, comprising: 4.4% audium croscarmellose; and 4.8% azithromycin dihydrate; 2.9% lubricant, 58.0% sucrose; 55. A desage form as defined in claim 14, comprising: 40 29.0% sorbitol: 58.2% azithromycin dihydrate; 1.9% anhydrous sodium carbonate: 3.1% maize starch; 0.4% sodium benzoute; 33.8% dibasic calcium phosphate, lactose, or microcrys-1.5% tragacenth gum powder, tallino cellulose; 1.5% titacium dioxide: 2.0% sodium starch glycolate or crosslinked polyvi-1.15% colloidal silicon dioxide; nylpyrrolidene; and 0.6% glycine; and 2.9% lubricant. 2.3% flavoring 56. A desage form as defined in claim 14, comprising: 63. A dosage form as defined in claim 17, comprising: 58.2% azithromycin dihydrate; 5.0% szithromycin dikydrate; 6.0% mains starch: 91.8% sucrose: 30.9% dibasic calcium phosphate, lactose, or microcrys-0.4% anhydrous tribasic sodium phosphate; talling cellulose: 0.2% hydroxypropyleellulose; 2.0% sodium starch glycolate or crosslinked polyvi- 55 nylpyrrolidone; and 0.2% aunthen gum; 0.1% colloidsi silicon dioxide; 2.9% lubricumt. 57. A dosage form as defined in claim 14, comprising: 0.6% glycine; 58.2% azithromycin dihydrate; trace coloring; and 11.1% make starch: 60 1.8% flavoring. 25.7% dibatic calcium phosphate, lactose, or microcrys-64. A douge form as defined in claim 17, comprising: talline cellulose; 5.0% azithromycia dihydrate; 2.0% sodium starch glycolate or crosslinked polyvi-92.5% sucrose; nylpymolidone; and 0.4% anhydrous tribasic sodium phosphate; 65 29% lubricant 0.3% sodium carboxymethylcellulose; 58. A dosage form as defined in claim 14, comprising: trace coloring: and

29 1.8% flavoring. 65. A dosage form as defined in claim 17, comprising: 5.0% azithromycin dihydrate; 90.4% sorbital; 1.8% anhydrous sodium carbonate: 0.3% sodium carboxymethylcethulose; 0.1% colloidal allicon dioxide: 0.6% glycine; trace coloring; and 1.8% flavoring. 66. A dosage form as defined in claim 17, comprising: 5.0% azithromycin dihydrate; 46.3% sorbitoi: 46.3% sucrosc: 0.4% anhydrous tribasic sodium phosphate; 0.2% hydroxypropylmethylcellulose: 0.2% ranthan gum; and trace coloring 1.2% flavoring. 67. A dosage form as defined in claim 17, comprising: 5.0% azithromycin dihydrate; 45.7% sucrose: 45.7% sorbitol; 0.9% anhydrous sodium carbonate; 0.2% anhydrous tribesic sodium phosphate; 0.1% hydroxypropylmethylcellulose: 0.1% zaethan gum; 0.1% sodium carboxymethylcellulose; 0.1% colloidal ailicon dioxide: 0.3% glycine; trace coloring; and 1.8% flavoring. 68. A dosage form as deflued in claim 22, comprising: 9.5% azithromycin dihydrate; 88,2% aucrosc; 0.8% anhydrous tribasic sodium phosphate; 0.5% colloidal silicon dioxide; and 0.9% flavoring. 69. A dosage form as defined in claim 22, comprising: 9.5% szithromycin dihydrate; 88.2% sorbitol: 0.8% anhydrous tribesic sodium phosphate; 0.5% colloidal silicon dioxide; and 0.9% flavoring. 70. A dosage form as defined in claim 22, comprising: 9.6% szithromycin dihydrate; 88.9% sucrose; 0.4% anhydrous tribasic sodium phosphate; 0.2% colloidal silicon dioxide; and 0.9% flavoring. 71. A dosage form as defined in claim 22, comprising:

9.3% azithromycin dihydrate;

16.7% azithromycia dihydrate;

2.0% colloidal silicon dioxide; and

1.8% anhydrous tribasic sodium phosphate;

72. A dosage form as defined in claim 22, comprising:

86.1% sucrose;

0.9% flavoring.

30 79.5% sucrose; 1.4% anhydrous tribasic sodium phosphate;

0.9% colloidal zilicon dioxide; and

1,6% flavoring.
73. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dihydrate;

44.1% sucrose:

44.1% sorbital:

0.8% anhydrous tribusic sodium phosphate;

0.5% colloidal allicon dioxide; and

0.9% flavoring.

74. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dibydrate;

44.1% sucrose:

44.1% sorbitol;

0.4% anhydrous tribusic sodium phosphate;

0.2% anhydrous audium carbonase;

0.2% glycine;

0.5% colloids silicon dioxide; and

0.9% flavoring. 75. A therapeutic package, comprising

a container,

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at oral desage form of azzithromycin which exhibits either or

(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with packlies turning at 100 rpm; and/or

(b) a value of (AUC,)(AUC,) of at least 0.80 with a lower 90% confidence limit of at least 0.75,

and, associated with said package, written matter nonlimited as to whether the dosage form can be taken with or without food.

76. A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a tablet.

77. A therapeutic package as defined in claim 75, wherein said desage form is in the form of a powder for oral

suspension.
78. A therapeutic package as defined in claim 77, wherein said dosage form is in the form of a suspension made from said powder.

79. A therapeutic package as defined in claim 75, wherein

said dosage form is in the form of a unit dose packet.

80. A therapeuric package as defined in claim 79, wherein said dosage form is in the form of a suspension made from said unit dose packet.

\$1. A method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an real desage form which exhibits either or both of:

(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the desage form equivalent to 200 mg of azithromycin is tosted as act forth in USP test ratus under conditions at least as stringent as the following: 900 ml actiom phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm; and/or

(b) a value of (AUC, V(AUC,) of at least 0.80 with a lower 90% confidence limit of at least 0.75.

31

- \$2. A method as defined in claim \$1, wherein said manural is a human.
- 23. A method as defined in claim 52, wherein said dosage form exhibits a value of (AUC, W(AUC,) of at least 0.80 with a lower 90% confidence limit of at least 0.75. 5
- 84. A method as defined in claim 82, wherein said dosage form is in the form of a tablet.
- 85. A method as defined in claim 82, wherein said dosage form is in the form of a powder for oral suspension.
- 86. A method as defined in claim 85, wherein said dosage 10 form is in the form of a suspension made from said powder.
- 87. A method as defined in claim \$2, wherein said dosage form is in the form of a unit dose packet.
- 88. Method as defined in claim 87, wherein said dosage form is in the form of a suspension made from said unit dose 15 packet.
- 89. A method as defined in claim 83, wherein said dosage form is in the form of a tablet,
- 90. A method as defined in claim 89, wherein said dosage form is in the form of a powder for oral suspension.
- 91. A method as defined in claim 90, wherein said dosage form is in the form of a suspension made from said powder.

- 32
- 92. A method as defined in claim 83, wherein said dosage form is in the form of a unit dose packet.
- 93. A method as defined in claim 92, wherein said dosage form is in the form of a suspension made from said unit dose packet
- 94. A package as defined in claim 75, wherein said dosage form exhibits a value of (AUC_{pa})/(AUC_{pa}) of at least 0.80 with a lower 90% confidence limit of at least 0.75.
- 95. A package as defined in claim 94, wherein said dosage form is in the form of a tablet.
- 96. A package as defined in claim 94 wherein said dosage form is in the form of a powder for oral suspension.
- 97. A package as defined in claim 96, wherein said dosage form is in the form of a suspension made from said powder.
- 96. A package as defined in claim 94, wherein said dosage form is in the form of a unit dose packet.
- 99. A package as defined in claim 98, wherein said dosage form is in the form of a suspension made from said unit dose 20 packet.

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EXHIBIT B

(12) United States Patent Allen et al.

(10) Patent No.:

US 6,268,489 B1 Jul. 31, 2001

(45) Date of Patent:

(54)	AZITHR	OMYCIN DIHYDRATE	(56) References Cited	
(75)	Inventors:	Douglas J. M. Allen, New London; Kevin M. Nepveur, Old Saybrook, both of CT (US)	U.S. PATENT DOCUMENT 4,020,270 4/1977 Arcamose et al	536/18
(73)	Assignee:	Pfizer Inc., New York, NY (US)	4,219,541 * 8/1980 Deposato et al 4,474,768 * 10/1984 Bright 4,512,982 * 4/1985 Hauske et al 4,517,359 5/1985 Kobrekel et al	514/29
(*)	Notice;	Subject to any disciaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	4,526,889 7/1985 Bright	514/20
(21)	Appl. No.:	07/994,040	Pelizza et al., Parmaco-Ed.Sc., 31, 254-26	2 (1976).
(22)	Filed:	Dec. 21, 1992	Allen et al., J. Phann. Sci., 67, 1087-1093	(1978).
			 cited by examiner 	
	Rel	sted U.S. Application Data	Primary Examiner-Elli Peselev	
(63)	Continuation 11, 1989, no	a of application No. 07/449,961, filed on Dec.	(74) Attorney, Agent, or Pirm—Peter C. Ric C. Benson; Mervin E. Brokke	bardson; Gregg
(30)	Foreig	n Application Priority Data	(57) ABSTRACT	
	Int. Cl.?	(WO) PCT/US87/01612 C87H 17/08	Non-hygroscopic, azithromycin (9-dec methyl-9a-homoerythromycin) dihydrate therefor.	xo-9a-aza-9a- and a process
(58)	Field of Se	arch 536/7.4, 18.5	3 Claims, No Drawings	

US 6,268,489 B1

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AZITHROMYCIN DIHYDRATE

This is a continuation of application Ser. No. 07/449,961, filed on Dec. 11, 1989 now abandoned as a request for U.S. 5 examination of International Application No. PCT/US87/01612, filed Jul. 9, 1987.

BACKGROUND OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A), viz., a non-hygroscopic dihydrate 15 form thereof.

Azithromycin is the U.S.A.N. (generic name) for ²⁰ 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, a broad spectrum antibacterial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. The name "N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A" was employed in these patents. The present more systematic name is based upon the ring expansion and replacement nomenclature of the "IUPAC Nomenclature of Organic Chemistry, 1979 Edition," Pergamon ³⁰ Press, 1979, pp. 68–70, 459, 500–503.

As previously crystallized from ethanol and water (e.g., 35 Example 3 of U.S. Pat. No. 4,474,768), azithromycin was obtained as a hygroscopic monohydrate (for details, see Preparation 1 below). Because of its hygroscopic nature, it is most difficult to prepare and maintain this prior monohydrate product in a form having a constant, reproducible water-content. It is particularly difficult to handle during formulation, since at higher relative humidity levels which are generally required to avoid electrostatic problems (e.g., flow rates, dusting with potential for explosion), the monohydrate readily picks up varying amounts of water, the amount depending upon exposure time and the precise value of the relative humidity (see Preparation 1 below). Such problems have been overcome by the present invention of a stable dihydrate which is essentially non-hygroscopic under 50 conditions of relative humidity conductive to formulation of azithromycin.

SUMMARY OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin, viz., a crystalline, non-hygroscopic dihydrate, prepared by crystallization from tetrahydrofuran and an aliphatic (C_3-C_7) hydrocarbon in the presence of at least two molar equivalents of water.

2 Azithromycin is of the formula

It is derived from erythromycin A without involvement of asymmetric centens, and so has stereochemistry at each of these centens (*) which is identical with that of erythromycin A. Named systematically as an erythromycin A derivative, the compound is called 9-deoxo-9a-aza-9a-mothyl-9a-bomoerythromycin A. Azithromycin, including the present dihydrate, possess broad-spectrum antibacterial activity useful in the treatment of susceptible bacterial infections in mammals, including man.

The expression "aliphatic (C₅-C₇)hydrocarbon" refers to lower boiling hydrocarbon solvents, frequently mixtures of particular boiling point ranges such as those generally referred to as "pontane", "hexane", "hexanes", etc., but which may also be substantially pure, e.g., n-hexane, cyclohexane or methylcyclohexane. A preferred hydrocarbon solvent is so-called "hexane", having a boiling point which ranges near that of pure n-hexane.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is readily carried out. Azithromycin, prepared according to Bright or Kobrehel et al. (cited above) in amorphous form, or as the monohydrate (which may contain, because of its hygroscopicity, more than one molar equivalent of water) is dissolved in tetrahydrofuran. Since the temperatures required for the initial stages of the present process are not critical, ambient temperatures are generally employed, avoiding the cost of heating and cooling. Furthermore, to maximize yield and minimize solvent, labor and equipment costs, the volume of tetrahydrofuran is kept to a near minimum, e.g., 2 liters of solvent per kilogram of substrate. Any insoluble impurities which may be present at this stage are readily removed by conventional methods of filtration. If necessary, the mixture can be decolorized with activated carbon. If desired, the highly concentrated mixture can be diluted with a portion of (C5-C7) by drocarbon prior to filtration, in order to facilitate handling. If the water content of the ingoing bulk is much greater than one molar equivalent, e.g., approaching 2-molar equivalents, it is preferable to dry the mixture for a short period of time over a drying agent such as MgSO4, particularly if hydrocarbon solvent is to be added prior to filtration. To obtain the crystalline dihydrate, water is added to the resulting clear solution, in an amount sufficient to bring the total water content to a level corresponding to at least two molar equivalents, generally not exceeding a level of about 3-4 molar equivalents. The level of water present in the

US 6,268,489 B1

3

system is readily monitored by standard Karl Fischer titration. The addition of water is followed by the addition of the hydrocarbon solvent (or of more hydrocarbon solvent, if the mixture was previously diluted before filtration), leading to crystallization of the desired dihydrate product. This stage of the process can be carried out at ambient temperature (e.g. 17-30° C.), but to facilitate the initial crystallization, is preferably carried at slightly elevated temperature (e.g. 30-40° C.). The total volume of hydrocarbon solvent employed is generally at least about four times in volume 10 that of the tetrahydrofuran. Higher volumes of hydrocarbon are satisfactory, but are generally avoided in the interest of minimizing cost. Once crystallization is complete, the product is recovered by filtration, usually after a period of granulation (e.g., 3-24 hours) at ambient temperature. The 15 product is usually vacuum dried of organic solvents (at 20-40° C., conveniently at ambient temperature). To avoid loss of water of hydration, the volatiles and water-content are generally monitored during drying, such that the level of tetrahydrofuran and hydrocarbon will generally fall below 20 0.25% and the water content will be within 0.3% of theory (4.6%).

Azithromycin dihydrate is formulated and administered in the treatment of susceptible bacterial infections in man according to methods and in amounts previously detailed by ²⁵ Bright, U.S. Pat. No. 4,474,768, cited above and hereby incorporated by reference.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

EXAMPLE 1

Non-Hygroscopic Azithromycin Dihydrate

Method A

The hygroscopic monohydrate of Preparation 1 (100 g; water-content:3.1%), tetrahydrofuran (220 ml) and diatomaceous earth (5 g) were combined in a 500 ml Erlemmyer flask, stirred for 30 minutes and filtered with 20 ml of tetrahydrofuran wash. The combined filtrate and wash was transferred to a 3 liter round bottom flask. The solution was stirred vigorously and H₂O (2.0 ml) was added. After 5 minutes, hexane (1800 ml) was added over 5 minutes, with continued vigorous strings. Following an 18 hour granulation period, title product was recovered by filtration with 1×10 ml hexane wash, and dried in vacuo to 4.6±0.2% H₂O by Karl Fischer, 89.5 g.

Method B

The hygroscopic monohydrate of Preparation 1 (197.6 g) 50 and tetrahydrofuran (430 ml) were charged to a reactor and the mixture stirred to achieve a milky white solution. Activated carbon (10 g) and diatomaceous earth (10 g) were added and the mixture stirred for 15 minutes, then diluted with 800 ml of bexane and filtered with suction over a pad of diatomaceous earth with 250 ml of hexane for wash. The combined filtrate and wash was diluted to 2500 ml with bexane and warmed to 34° C. With stirring, 24.7 ml of H₂O was added. The mixture was allowed to cool to room temperature, granulated for five hours and title product 50 recovered and dried as in Method A, 177.8 g.

The dihydrate melts sharply at 126° C. (hot stage, 10°/minute); differential scanning calonimetry (heating rate, 20° C/minute) shows an endotherm at 127° C; thermal gravimetric analysis (heating rate 30° C/minute) shows a 1.80° weight loss at 150° C; ir (KB) 3953, 3553, 3488, 2968, 2930, 2888, 2872, 2827,

4

2780, 2089, 1722, 1664, 1468, 1426, 1380, 1359, 1344, 1326, 1318, 1282, 1270, 1252, 1187, 1167, 1157, 1123, 1107, 1082, 1050, 1004, 993, 977, 955, 930, 902, 986, 879, 864, 833, 803, 794, 775, 756, 729, 694, 671, 661, 637, 598, 571, 526, 495, 459, 399, 374, 321 and 207 cm⁻¹; [alpha]²⁶_D=41.4° (c=1, CHCl₂).

Anal. Calcd. for C₃₈H₇₂N₂O₃₂.2H₂O: C, 58.14; H, 9.77; N, 3.57; OCH₃, 3.95; H₂O, 4.59. Found: C, 58.62; H, 9.66; N, 3.56; OCH₃, 4.11; H₂O, 4.49. Neutralization Equivalent (0.5N HCl in 1:1 CH₃CN:H₂O): Calcd.: 374.5. Found: 30.2.4

Samples of a dihydrate, slightly over dried to contain 4.1% water (less than theoretical) rapidly picked-up water at 33%, 75% or 100% relative humidities to achieve the theoretical water content (4.6%) for the dihydrate. At 33% and 75% relative humidities, water content remained essentially constant for at least 4 days. At 100% relative humidity, the water content further rose to about 5.2, where it remained essentially constant of the next three days.

A sample of the same dihyrate, maintained at 18% relative humidity gradually lost water. At four days, the water content was 2.5% and at 12 days, 1.1%.

PREPARATION 1

Hygroscopic Azithromycin Monohydrate

Substantially following the methylation procedure of Kobrebel et al., U.S. Pat. No. 4,517,359; and the crystalli-zation procedure of Bright, U.S. Pat. No. 4,474,768; 9-deoxo-9a-aza-9a-homocrythromycin A (previously called 11-aza-10-deoxo-10-dihydrocrythromycin A; 100 g, 0,218 mol) was dissolved with stirring in 400 ml CHCl₃. Formic 35 acid (98%; 10.4 ml, 0.436 mol) and formaldehyde (37%; 16.4 ml, 0.349 mol) were added over 4-5 minutes, and the mixture heated at reflux for 20 hours. The mixture was cooled to ambient temperature, diluted with 400 ml H₂O and adjusted to pH 10.5 with 50% NaOH. The aqueous layer was separated and extracted 2x100 ml with fresh CHCl. The organic layers were combined, stripped in vacuo to 350 ml, twice diluted with 450 ml of ethanol and restripped to 350 ml, and finally diluted with 1000 ml H2O over a 1 hour period, pausing for 15 minutes as a slurry began to develop after the addition of about 250 ml of H₂O. Title product was recovered by filtration and dried in air at 50° C. for 24 hours, 85 g; mp 136° C.; differential thermal analysis (heating rate 20° C./minute) shows an endotherm at 142° C.; thermal gravimetric analysis (heating rate 30° C./mimte) shows a 2.5% weight loss at 100° C. and a 4.5% weight loss at 150° C.; water content 3.92%; ethanol content 1.09%.

Anal. Calcd. for C₅₀H₇₂N₂O₅₂ (corrected for ethanol and water content): C, 58.46; H, 9.78; N, 3.74; Alkoxy, 4.57. Found: C, 58.40; H, 9.29; N, 3.50; Alkoxy, 4.52.

A sample of the monohydrate (having a water content of 3.2%) was maintained at 1.8% relative humidity for 14 days. The sample lost water over the first 24 hours to yield monohydrate having the theoretical water content (2.35%). The water content then remained substantially constant over 14 days, a value of 2.26% being recorded at 14 days.

At 33% relative humidity the water content of a sample of the same monohydrate rapidly rose to 5.6% where it remained substantially steady for at least three days. Similarly at 75% and 100% relative humidity, the water content rose rapidly, but was now maintained at even higher levels, 6.6% and 7.2%, respectively, for at least 3 days.

US 6,268,489 B1

5

What is claimed is: 1. Crystalline azithromycin dihydrate.

2. A method of preparing crystalline azithromycin dihydrate which comprises crystallization of amorphous azithromycin or azithromycin monohydrate from a mixture of

6 tetrahydrofuran and a (C_3-C_7) aliphatic hydrocarbon in the presence of at least 2 molar equivalents of water.

3. A method of claim 2 wherein the hydrocarbon is

bexanc.

EXHIBIT C



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August 5, 2003

By Hand

Jeffrey B. Kindler, Esq.
Senior Vice President and General Counsel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5575

Re: Azithromycin - U.S. Patent Nos. 5,605,889 and 6,268,489

Dear Mr. Kindler:

We represent Teva Pharmaceuticals USA, Inc ("Teva"). We write concerning U.S. Patent Nos. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," and 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," both of which are assigned on their face to Pfizer, Inc.

On December 12, 2002, Teva filed with the FDA Abbreviated New Drug Application ("ANDA") No. 65-153 for 250 mg azithromycin tablets. On November 27, 2002, Teva filed ANDA No. 65-150 for 600 mg azithromycin tablets. Teva expects the FDA to approve these ANDAs in due course.

By filing these ANDAs, Teva has made substantial preparations to make, use, offer to sell, sell, and/or import a generic version of ZITHROMAX. By filing these ANDAs with the intent to obtain approval to market prior to the expiration of the '489 and '889 patents, Teva has committed a technical act of infringement of these patents. In light of these activities, Teva requests that Pfizer grant a covenant to Teva that Pfizer will not enforce the '889 and '489 patents against Teva for having made, making, using, offering for sale, selling, or importing the azithromycin tablets described in Teva's ANDA Nos. 65-153 and 65-150.

Pfizer has sued Novopharm, Teva's Canadian affiliate on the Canadian equivalent of the '489 patent. Based on the information available to Pfizer as a result of that suit, Teva believes that Pfizer has sufficient information to determine whether it believes Teva's manufacture, use, importation, or sale of the azithromycin products covered by the ANDAs infringe the '889 and/or '489 patents. However, should you require further information, Teva will provide to Pfizer, upon execution of an appropriate confidentiality agreement, information regarding the formulation of the products described in Teva's ANDAs, the bioequivalency data included in the ANDAs, and samples of (i) the products described in the ANDAs, (ii) the raw materials used to make those products, and (iii) azithromycin ethanolate monohydrate, the active ingredient in the products described in the ANDAs.

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Mr. Jeffrey B. Kindler August 2, 2003 Page 2 of 2



We are prepared to send Pfizer these materials immediately upon execution of an appropriate confidentiality agreement. For your convenience, we attach a form confidentiality agreement. However, we will disclose these materials under any reasonable terms. If our letter is unsatisfactory, please propose an acceptable alternative.

In view of the urgent need to resolve issues of potential patent infringement prior to Teva's marketing of its azithromycin products, we ask that you respond to this letter within forty five (45) days of receipt. If we do not receive a reply within this time frame, we will take appropriate legal action.

Very truly yours,

Steven J. Lee

.cc: Richard Egosi, Esq.

Enclosure

CONFIDENTIALITY AGREEMENT

This Confidentiality Agreement is executed by and between TEVA Pharmaceuticals USA ("Teva"), PFIZER, INC. ("Pfizer"), and Counsel therefore.

RECITALS

WHEREAS, pursuant to § 505(j), Title 21 of the Federal Food, Drug and Cosmetic Act ("the Act"), Teva has filed abbreviated new drug applications, ANDA Nos. 65-153 and 65-150, to obtain approval to engage in the commercial manufacture, use, sale, and importation of azithromycin before the expiration of U.S. Patent Nos. 5,605,889 ("the '889 patent") and 6,268,489 ("the '489 patent").

WHEREAS, Pfizer owns the '889 and '489 patents.

WHEREAS, Pfizer manufactures and markets a pharmaceutical product called Zithromax® (azithromycin) and owns and/or controls certain patent rights, trademarks and know-how relating thereto, including the '889 and '489 patents.

WHEREAS, by letter dated August 5, 2003, Teva offered Pfizer certain confidential information of Teva with respect to ANDA Nos. 65-153 and 65-150 and the product Teva proposes to sell thereunder ("Teva Confidential Information") to allow Pfizer to evaluate whether it believes the commercial manufacture, use, sale, or offer for sale in the United States, or the importation into the United States of the azithromycin products described in its ANDAs will infringe, contribute to or induce the infringement of the '889 and '489 patents.

WHEREAS, Teva will provide Counsel for Pfizer with sufficient of Teva's Confidential Information to permit them to conduct an evaluation under appropriate confidentiality provisions as set forth herein.

NOW THEREFORE, in consideration of the mutual covenants herein contained, the parties mutually agree as follows:

- 1. Teva shall promptly provide to Counsel for Pfizer a copy of documents sufficient to describe in detail formulation of Teva's proposed azithromycin product, including but not limited to the components of the formulation, the percentage of each component used in the formulation and the process by which Teva prepares the proposed azithromycin product; one (1) 50 tablet sample from each lot of Teva's azithromycin tablets, including 250 mg and 600 mg, including one (1) 50 tablet sample from each lot which was submitted to the FDA, or as to which information was submitted to the FDA in connection with ANDAs 65-153 and 65-150, as well as samples of the raw materials used to make those tablets; and the bioequivalency data included in ANDA Nos. 65-153 and 65-150.
- 2. Counsel for Pfizer shall use the Teva Confidential Information referenced in Paragraph 1 herein for the sole purpose of evaluating whether it believes the commercial

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manufacture, sale, or offer for sale within the United States, or the importation into the United States, of the azithromycin products described in ANDA Nos. 65-153 and 65-150 will infringe, contribute to, or induce the infringement of the '889 and '489 patents. At the conclusion of such evaluation, but in no event later than September 19, 2003, Counsel for Pfizer shall destroy or return all Teva Confidential Information.

- 3. Counsel for Pfizer may not disclose Teva's confidential information to Pfizer or any other party, except that Counsel for Pfizer may disclose the physical samples to Pfizer employees for the purpose of conducting in vitro tests, and may disclose any of the confidential information, including the physical samples, to independent experts not associated with Pfizer. Such experts must first be identified to Teva, and Teva must have 5 business days within which to object to such experts. Such experts must be made aware of this agreement and must agree to abide by its terms. Counsel for Pfizer agrees to not disclose, communicate or cause to be communicated to any third party, in any manner whatsoever, any and all of the Teva Confidential Information without receiving the prior written consent of Teva to use such Confidential Information. Counsel for Pfizer will not disclose any of Teva's Confidential Information for any reason whatsoever except as set forth above. Samples of Teva's azithromycin and azithromycin products are not yet approved for marketing in the United States, and may not be administered to human patients or subjects.
- 4. Counsel for Pfizer shall have no obligation to Teva under this Agreement to maintain the confidentiality of information that:
- a. can be demonstrated to have been in the public domain prior to execution of this Agreement;
- b. can be demonstrated to have been in possession, either through independent development or from another source not under obligation of secrecy to Teva prior to disclosure of Teva's Confidential information under this Agreement; or
- c. becomes part of the public domain by publication or otherwise, not due to any unauthorized acts by Counsel for Pfizer.
- 5. Counsel for Pfizer, and any independent experts retained by them, agree to maintain the confidentiality of all of Teva's Confidential Information received under the terms of this Agreement unless instructed otherwise by Teva in writing.
- 6. This Agreement constitutes the entire agreement between the parties and supersedes all previous agreements and understandings relating to the subject matter hereof. This Agreement can only be modified by a writing signed by both parties hereto.
- 7. This Agreement may be executed by facsimile signatures and/or in counterparts and will become effective upon the date execution has been made by the last party whose execution is required, each such counterpart of which shall be an original, but all of which constitute one agreement.

ACCEPTED AND AGREED TO:
PFIZER, INC. By: Title:
Date:
TEVA PHARMACEUTICALS USA, INC.
Ву:
Title:

EXHIBIT B

ORIGINAL

IN THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC.,	
Plaintiff,	
v. (Civ	ivil Action No. 4979
PFIZER INC.,	04 ev 4979
Defendant.	

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), for its Complaint against Pfizer Inc. ("Pfizer"), alleges as follows:

THE PARTIES

- 1. Teva is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090. Teva is a developer, manufacturer, and marketer of generic and other pharmaceutical products in the United States.
- On information and belief, Pfizer is a Delaware corporation with its principal place of business at 235 East 42nd Street, New York, New York, 10017-5575.
- 3. On information and belief, Pfizer owns U.S. Patent No. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," a copy of which is attached hereto as Exhibit A.
- 4. On information and belief, Pfizer owns U.S. Patent No. 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," a copy of which is attached hereto as Exhibit B.
- On information and belief, Pfizer holds New Drug Application ("NDA") No. 50 784 for ZITHROMAX* 500 mg azithromycin dihydrate ("azithromycin") tablets.

JURISDICTION AND VENUE

- 6. This Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 et seq.
- 7. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction seeking a declaratory judgment that the '889 and '489 patents are invalid and not infringed.
- 8. Personal jurisdiction exists over the defendant because defendant has its principal place of business within this district, and because defendant does business within this district.
 - 9. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and 1400(b).

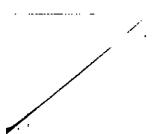
THE PRESENCE OF AN ACTUAL CONTROVERSY

- 10. Pfizer markets in the U.S. an oral antibiotic under the trade name ZITHROMAX[®]. The active ingredient in ZITHROMAX[®] is azithromycin. In its 2002 Annual Report, Pfizer reported sales of ZITHROMAX of over \$1.5 billion. In its 2003 Annual Report, Pfizer reported sales of ZITHROMAX of over \$2 billion.
- 11, On October 9, 2003, Teva filed Abbreviated New Drug Application ("ANDA") Number 65-193 ("ANDA No. 65-193"). ANDA No. 65-193 is directed to a generic version of ZIIIIROMAX \$\infty\$ 500 mg tablets. By preparing and filing this ANDA, Teva has made substantial preparation to make, use, import, offer to sell, and sell a generic version of 500 mg ZITHROMAX® tablets in the U.S.

- 12. Pfizer's '889 and '489 patents contain claims directed to azithromycin. On information and belief, Pfizer will bring suit against Teva, alleging infringement of the '889 and '489 patents, if Teva commercially markets generic versions of 500 mg ZITHROMAX [©] tablets.
- 13. Pfizer has demonstrated a willingness and intention to enforce foreign patents that are related to ZITHROMAX. Pfizer initiated proceedings in Canada against Novopharm, an affiliate of Teva, asserting the Canadian equivalents to the '489 and '889 patents. Pfizer Canada and Pfizer Inc. v. Novopharm, Federal Court Trial Division, Ontario, Court File No. T-74-03; Pfizer Canada and Pfizer Inc. v. Novopharm, Federal Court Trial Division, Ontario, Court File No. T-2448-03. In addition, Pfizer has initiated proceedings against other entities that have indicated an intention to market generic equivalents of ZITHROMAX.
- 14. Moreover, Pfizer previously refused to grant Teva a covenant that it will not enforce the '889 and '489 patents against Teva. On November 27, 2002 and December 12, 2002, Teva filed ANDA Nos. 65-150 and 65-153, respectively, seeking approval to market generic versions of 250 mg and 600 mg ZITHROMAX. On August 5, 2003, Teva hand delivered to Pfizer a letter ("the August 5, 2003 letter") requesting a covenant that Pfizer will not enforce the '889 and '489 patents against Teva. (A copy of the August 5, 2003 letter is attached as Exhibit C.) Teva requested that Pfizer respond to the August 5, 2003 letter within forty-five days of receipt. Pfizer did not respond within the forty-five days, and indeed Teva has received no response from Pfizer to date.
- 15. On September 22, 2003, Teva filed suit against Pfizer in this Court, seeking a declaratory judgment of invalidity of the '889 and '489 patents, and/or a declaratory judgment of noninfringement with regard to Teva's generic version of ZITHROMAX[®] 250 and 600 mg tablets. This suit is currently pending under Civil Action No. 03CV7423 (LAP)(AJP).

- generic competition from Teva by attempting to enforce its patents against other products of Teva. On at least five occasions, Pfizer (or its predecessor) sued or maintained suit against Teva (or its related entities) for patent infringement relating to other drugs for which Teva has filed an ANDA: (i) Pfizer Inc. and Pfizer Technologies Ltd. v. Novopharm Ltd., 00-cv-01475 (N.D. Ill.), concerning fluconazole; (ii) Pfizer Inc./Warner-Lambert v. Teva, 00-cv-4589 and 00-cv-4168 (D.N.J.), concerning gabapentin; (iii) Schwarz Pharma, Inc., Schwarz Pharma AG and Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc., 01-cv-4995 (D.N.J.), concerning moexipril; (iv) Bayer and Pfizer v. Biovall & Teva, 01-cv-1205 and 01-cv-1206 (D.P.R.), concerning nifedipine; and (v) Warner-Lambert v. Teva USA, 99-cv-0922 (D.N.J.), concerning quinipril.
- 17. In view of Pfizer's previous refusal to grant Teva a covenant that it will not enforce the '889 and '489 patents against Teva, Pfizer's proceedings against Teva's affiliate and others to enforce the Canadian equivalent of the '489 and '889 patents, and Pfizer's pattern of aggressively enforcing its patents in an attempt to prevent generic competition by Teva, Teva is under a reasonable apprehension that Pfizer will sue Teva, alleging infringement of the '889 and '489 patents.
- 18. To avoid legal uncertainty and to protect its substantial investment (and anticipated future investments) in its manufacturing process for its generic 500 mg

 ZITHROMAX® product, Teva has instituted this declaratory judgment action.



COUNT I DECLARATORY JUDGMENT OF NONINFRINGEMENT

19. Teva's commercial manufacture, use, offer for sale, sale, or importation of its 500 mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, would not infringe any properly construed claim of the '889 patent.

COUNT II DECLARATORY JUDGMENT OF NONINFRINGEMENT

Teva's commercial manufacture, use, offer for sale, sale, or importation of its 500 20. mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, would not infringe any properly construed claim of the '489 patent.

COUNT III DECLARATORY JUDGMENT OF PATENT INVALIDITY

21. The claims of the '889 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

COUNT IV DECLARATORY JUDGMENT OF PATENT INVALIDITY

22. The claims of the '489 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

PRAYER FOR RELIEF

 $\label{eq:wherefore} WHEREFORE_{I^*} Teva\ respectfully\ requests\ the\ Court\ enter\ judgment\ against\ Pfizer\ to$ include:

- A. A declaration that Teva's manufacture, use or sale of its 500 mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, will not infringe United States Patent No. 5,605,889;
- B. A declaration that Teva's manufacture, use or sale of its 500 mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, will not infringe United States Patent No. 6,268,489;
 - C. A declaration that United States Patent No. 5,605,889 is invalid;
 - D. A declaration that United States Patent No. 6,268,489 is invalid;

By:

- E. An award of Teva's reasonable costs and attorneys' fees in connection with this action; and
 - F. All such other and further relicf as the Court may deem just and proper.

Respectfully submitted,

KENYON & KENYON

Dated June 23, 2004

Steven J. Lee (SL1043)

Elizabeth J. Holland (EH0850)

Cynthia M. Lambert (CL2281)

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New York, NY 10004

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Fax: (212) 425-5288

Counsel for Plaintiff.

TEVA PHARMACEUTICALS USA, INC.

United States Patent [19]

Curatolo et al.

[11] Patent Number: 5,605,889 [45] Date of Patent: Feb. 25, 1997

[54] METHOD OF ADMINISTERING AZITHROMYCIN

[75] Inventors: William J. Curatolo, Nigntic; George II. Foulds, Waterford, both of Conn.; Hylar L. Friedman, Brattleboro, Vt.

[73] Assignee: Pfizer Inc., New York, N.Y.

[21] Appl. No.: 235,069

[22] Filed: Apr. 19, 1994

(51) Int. CL^a A61K 31/70; A61K 9/14; A61K 9/20 (52) U.S. Cl. 514/29; 514/960; 424/464;

[56] References Clied

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4.382,045	\$/1983	Scievolino et al
4,474,768	10/1984	Bright
4,517,359	5/1985	Koluchel et al. , 536/7.4
4,963,531	10/1990	Remington 514/29
5,250,518	10/1993	Kobrehel et al 514/29
5,350,839	9/1994	Auska et al

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0307128 3/1989 Europeun Pat. Off. . 0582396 2/1994 Europeun Pat. Off. .

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Curatolo et al. J. Pharm. Sci., vol. 77 (4), pp. 322-324, (1988).
Welling et al. J. Pharm. Sci., vol. 67 (6), pp. 764-766, (1978).

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Hopkins, S., Am. J. Med., 91 (Suppl 3A), 405-455 (1991).

Toothaker et al., Ann. Rev. Pharmacol. Toxicul. vol. 20, 173-199, 1980.

Russell'et al., Pharmaccutical Research, vol. 10, No. 2, 187-196, 1993.

CA Abstracts: vol. 120:38194a; 1994.

Zithromax (Trademark of Pfizer, Inc.) Capsules Packago Insert for anthromycin capsule dosage form sold commercially in U.S.

Primary Examiner—John Kighi Assistant Examiner—Howard C. Loc Autorney, Agent, or Firm—Peter C. Richardson; Gregg C. Benson; James T. Jones

57) ABSTRACT

An oral desage form of azithromycin which does not exhibit an adverse food effect; Specific azithromycin oral desage forms including tablets, powders for oral autoensions and unit does puckets; Methods of treating interoblal infections with the desage forms; And therapeutic packages containing the desage forms.

99 Claims, No Drawings

METHOD OF ADMINISTERING AZITHROMYCIN

This invention relates to a desage form of azithromycin, and also to a method of treating a microbial infection which is lovelyes administering azithromycin, in the fed state to a manufactural, including a human pattern, in need of such treatment

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 98-aza-98-methyl-9-deoxe-9a-homocrythromycin A, a brusal spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly unzful as antibiotics.

In general, it is known that the absorption and bloavailability of any particular therapeutic agent can be affected by numerous factors when dosed orally. Such factors include the presence of food in the gastrointestinal (GI) tract because, in general, the gastric residence time of a drug is usually significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug is affected beyond a certain point due to the presence of food in the GI tract, the drug is said to exhibit a "food effect". Food effects are important insamuch as, when a drug exhibits an adverse food effect, there is risk associated with administering It to a patient who has easen recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the polot that the patient risks insufficient absorption to remediate the condition for which the drug was administered.

Other factors can also be involved in drug biografilability, the following being a non-comprehensive listing:

- (1) The particular desege form can affect binavallability. For example, the gastric residence time of a tablet or capsule can be significantly longer than that of a suspension, and the difference may wary depending on whether the subject has extend or is faited.
- (2) The pH of the stomach varies, between the fed and fasted state, with the amount of food therein, and drugs which are decomposition-sensitive to pH can be affected 45 accordingly.
- (3) The capacity of the liver to metabolize an absorbed drug (so-called "first pass" metabolism) may vary with the type of meal eaten. For example some vegetables (such as brussels aprouts) can almulate first pass metabolism of some drugs, but not others. Grapeffull julce, on the other band, may tabibit first pass metabolism of some drugs.
- (4) Bile, which is released from the gallbladder into the small intestine when a meal is ingested, has the ability to 59 solubilize poorly soluble drugs and thus increase blosvailability.

Additional factors can also be involved in the absorption and bioavailability of a particular drug, and absorption can actually be increased as well as decreased. These additional factors include, for example, pH-dopendent solubility, site-specific inestinal permeation rate, instability to intestinal cutymes, susceptibility to first pass metabolism, and inatability to colonic bacteria. Given the pleshora of factors which can influence bloavailability, there usually is no way to predict, in the absence of actual testing, whether a particular drug will entible a food effect. For example, Toothaker and

Weiling, Ann. Rev. Phormacol. Toxicol., 1980, 173-99, discuss various drugs whose absorption is delayed in the presence of lood (cephalexia, cefselor, metronidazole, aspi-

nis, alcolemac, indoprolen, digoxin, cimeldine), whose absurption may be unaffected by food (ampicillin, crythromycin estolate, spiramycin, propylthiouracil, oxazepam, hardroftunchiazide), and whose absorption is increased in the presence of food (crythromycin ethylsuccinate, hittofuration, 8-methoxasien, propranalol, metoprolot, dicoumarol, diszepam, bydrochlorothiazide).

As a further example, there appears to be no clear or definitive support for the proposition that tablets might exhibit fewer food effects than capsules, or vice-versa. Toothaker and Welling review studies which demonstrate food related reduced absorption for tablet design forms of crythromycin stearate, aspirin, patfellin, and setalol.

In the cuse of azithromycin, as lesst one (unpublished) study has shown that the absorption of azithromycin can be adversely affected if the patient is in a fed taste, and it has heartsfore been conventional wisdom that azithromycin capsule dosage forms exhibit a so-called adverse "food effect". Accordingly, in countries where azithromycin is currently available for use in the treatment of human patients, the product is sold with the specific direction that it be administered only in the fasted state, i.e. at loss one hour before or two hours following a secal.

It would accordingly be useful if azithromycin could be adminiated to patients that have eaten recently and also if a dosage form for azithromycin were available which could be administered to patients that have eaten, as well as patients to a fasted state.

SUMMARY OF THE INVENTION

This invention provides an ural dosage form of azithromych which can be administered to a mammal (including human) that has eaten and which exhibits substantially no adverse food effect, excluding any dosage form which contains a significant amount of an alkaline earth oxide or hydroxide. The dosage form exhibits a mean (AUC_{pa}) (AUC_{pa}) at least 0.80 with a lower 90% confidence limit of at least 0.75, the terms "(AUC_{pa})/(AUC_{pa})" and "90% confidence limit" being fully defined below.

In a further aspect, this invention provides a specific oral azithromycin dosage form which does not exhibit an adverse food effect. The dosage form comprises azithromycin and a pharmscentically acceptable carrier, as hereinafter further detailed and described. The desage form is in the form of a tablet (including both awallowable-only and chewable forms), in the form of a unit dose packet (sometimes referred to in the art as a "sachet"), in the form of a suspension roade from a unit dose packet, in the furm of a powder for oral suspension, and in the form of an oral suspension per se, it is noted that when a unit dose packet is constituted, it is probably mainly in the form of a mispensine if reconstituted according to directions, although the extent of suspension versus solution depends on a number of factors such as pH. The use of the term "suspension" herein is intended to embraco liquids containing azithromycin partially in sua-pension and partially in solution, and also totally in solution.

In a further aspect, this invention provides a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has search in need of such treatment, an antimicrobially effective annual of azilhromycin in an oral dosage form which exhibits substantially no adverse food effect. The dosage form amployed exhibits a

mean (AUC, with a lower 90% confidence limit of at least 0.75.

Reference herein and in the claims to a mammal (including humans) that has "exten" means that the mammal has eaten food of any sort within one hour prior to during up to Iwo hours after dosing.

In a further aspect, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycln which does not exhibit an adverse food effect contained therein, and, assoclated with said container, written matter non-limited as to whether the dosage form can be taken with or without food.

It is noted that powders for oral suspension and unit dose packets, of course, are not ingested directly by patients; rather, they are reconstituted in a suitable vehicle. These terms are nonetheless considered to be within the penumbra of the term "dosage form" for purposes of this invention.

Capsules as a dusage form do not form a part of the

For purposes of this invention azithromyclo may be administered alone or in combination with other therapeutic 20

A food effect can be detected and quantified as described, for example in Thothaker and Welling, supra, by determining the area under a curve (AUC) which plots the serum concentration (e.g., in ug/ml.) of axithromycin along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a pullent test population and are, therefore, mean values averaged over the entire test population. By measuring the area under the curve for a fed population of subjects (AUC_{feet}) and comparing it with the area for the same population of fusied subjects (AUC_{feet}), it can be determined whether a given drug exhibits an adverse

For definitional purposes of this invention, and specifi-cally with respect to azithromycin dosage forms only, a 35 dosage form of szibromycin exhibits an adverse food effect if, after dosing a population, once fasted and once fed, the mean (AUC_{pa})/(AUC_{pi}) is below the value 0.80 and/or the luwer 90% confidence limit for this ratio is below 0.75.

Convenely, a douge form of unithromycin which does 40 not exhibit an adverse food effect is one which, when tested not examini an adversa food effect is one which, when tested on a test population, exhibits a value for (AUC_{1,1,2})(AUC_{1,1,2}) of at least 0.80 and a lower 90% confidence limit for this value of at least 0.75. The value for mean (AUC_{1,1,2})(AUC_{1,2,1}) can have any value above 0.80 and still be within the scope of this invention, though it is preferred that it have an upper (mean) limit of 1.25, with an upper 90% confidence limit of

A population of "foil" subjects, for purposes of definition and for measuring AUC_{(con} is one made up of subjects each of whom has easen a Food and Drug Administration (FDA)-recommended standard high fat breakfast within a period of twenty minutes, and then ingested (i.e., awailowed) the test dosage form essentially immediately thereafter. A standard high-fat breakfast consists of, for example, two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown polatocs, two places of toust with two teaspounts of butter and two pats of jelly, and eight ounces of whole milk. This standard high-fig breakfast contains approximately 964 calories, 54% supplied as fat (58 gm) and 12% supplied as fat (58 gm) and 12% supplied as protein, calculated using the monograph "Nutritive Value of Foods", U.S. Department of Agriculture Home and Garden Bulletin Number 72. Additional food can also be command within the twenty minute period and the subject still qualifies as "fad". A "fasted subject" for purposes of definition and for measuring AUC_{pr} is one who has not eaten 65 for at least eight hours, typically overnight, prior to ingestion of the dosage form.

The 90% confidence limits on AUC_{fre}/AUC_{pa} for a particular population, in this case either a fed or a fasted population, can be (and were) calculated as described following using Schuirman's two one-sided test procedure.

The log-transformed AUCs were analyzed by means of an analysis of variance appropriate for a two-period, two-treatment crossover design. Analysis was eartied out using Statistical Analysis System (SAS) software from SAS Insti-tute, Cary, N.C. SAS procedure referred to in the SAS antiware as PROC GLM was used to determine sequence, subject within sequence, period and treatment (Fed/Fasted) effects. The sequence effect was tested using the (subject within sequence) mean square from the analysis of variance (ANOVA) as so error term. All other effects were tested against residual error (error mean square) from the ANOVA. The LSMEANS statement of SAS was used to calculate the least aquare means and their mandard errors and exvariances. These were used to obtain estimates for adjusted differences between treatment means and standard errors associated with these differences (log transformed).

The 90% confidence interval for two-way crossover design was constructed, based on these catimates, as the difference plus (or mires) the standard error of the difference times the 95th percentile of the t-distribution with (twice the sample size 2) degrees of freedom. The anti-log was taken on the limits to obtain the corresponding confidence for the

That is desage form according to the invention does not exhibit an adverse food effect is superising in view of the fact that azithromycin is unstable at low (acid) pH, on the order of the acidity encountered at the pH of stornach acid. The inventors have demonstrated that acidromycin breaks down if exposed to stomach juices which inherently exhibit soid pH. Thus, without being bound to any mechanism of action, it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention.

Commonly satigmed co-pending application Ser. No. 07/922,262 filed Jul. 30, 1992 discloses taste marking compositions of bitter pharmaceutical agents, such as analytic sutibiosics, containing, as a laste-masking component, a haste compound selected from the group consisting of alkaline such oxides and alkaline earth hydroxides. A comsikaling earth oxides and auguse earth nyammoer. A com-position of this invention, if it contains an alkaline earth unide or hydroxide at all, contains less than a tests-marking amount of the tasts-marking component. A composition of this invention therefore preferably contains less than about 1% of an alkaline earth oxide or hydroxide, and may be free of such teste-masking companent entirely.

DETAILED DESCRIPTION

Azithromycin is typically present in formulations according to the invention in an amount of from about 25 mg to about three grams, preferably 250 mg to two grams, for treatment of a human. If dosage forms are to be used for animal/veterinary applications, the amount can, of course, be adjusted to be outside those limits depending, for example, on the size of the animal subject being treated (e.g., a horse). The term "azithromycin" includes the pharmaceutically acceptable talts thereof, and also authydrous as well as bydrated forms. The azithromycin is preferably present as the dibydrate, disclosed, for example, in published European Patent Application 0 298 650 AZ.

In order to test whether a particular satisfromycia dounge form exhibits an adverse food effect, the most reliable method is actually to test the dounge form in vivo on a subject population, once fed and once fasted, determine the level of serum (or plasma) azithromycin with time, plot curves for the concentration of serum (or plasma) azithro30

mycin with time in each subject (fed and fasted) as described above, determine the area under each curve (conventionally, for example by simple integration) and finally determine whether the mean ratio (AUC, W(AUC,) exceeds 0.80, and whether the lower 90% confidence limit equals or exceeds

It is believed that the azithromyclit dosage forms of the It is believed that the anthromycin dosage turns of the invention do not exhibit a food effect in large part because they either provide arithromycin ready for dissolution in the Cl tract easendally immediately following ingestion (auspendons), or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution. While not wisting to be housed by theory, it is believed that if an azithromycin dosage form provides azithromycia immediately following logestion for dissolution in the Cl tract, or at least movides azithromycin for tion in the GI tract, or at least provides arithromyen for 13 disadurion within a certain time period following lagestion, the axishromsycin will be absorbed into the bloodstream at a rate which results in substantially no adverse food effect. In order for an adequate rate of absorption to occur, it is believed that the dosage form should provide azithromycin at a rate such that at least shout 90% of the azithromycin dissolves within about 30 minutes following ingestion, preferably within about 15 minutes following ingestion. A non-capsule desage form comprising azithromycin is also considered to full within the scope of the appended claims if it satisfies the in vitro dissolution testing requirements chamerated becam. An azithromycin dosuge form according to the invention exhibits at least about 90% dissolution of arithomycin within about 30 minutes, preferably within 15 minutes, when an amount of the dosage form equivalent to 200 mg of szishromycin is tested as set forth in USP test 200 mg of azihromycin is tented as set forth in USP test
'711> in a USP-2 dissolution apparatus under conditions at
least as stringent as the following: 900 ml approx. 0.1M
dibasic sodium phosphate buffer, pH 6.0, 37° C. with
paddies turning at 100 rpm. This test is described in US
Pharmacopeea XXII, pp., 1378-1579. Dosage forms which
pass this test under more stringent conditions (lower volume
of buffer, greater amount of dosage form, lower temperature,
have a realth apparatus at least the conditions. higher pH, lower paddle speed) are also included under the above definition. Any modifications to this test are also described herein. The time required for dissolution of a particular azithromycin dotago form in this in vitro test is believed to be an indicator of the time required for disco-belion of the dosage form in the GI environment. The following discussion is believed pertinent in this regard.

It is generally assumed and observed that the in vitro dissolution rate of dosage forms exhibits a rack order correlation with in vivo dissolution, particularly for a single dosage form type, e.g. tablets, which vary systematically in composition. Thus in vitro dissolution evaluation serves as important role in control of the quality of manufactured so dosage forms. It is not necessarily true that the in vitro dissolution rate is exactly the same as the in vivo dissolution rate. This is not surprising, since the smiticial conditions of an is vitro dissolution test (e.g. vessel geometry, mirring rate, stirring method, and so forth) are not identical to the conditions under which a dosage form disintegrates and dissolves in the GI trace

When comparing dosage forms of different type, e.g. cansules and tablets, in vitro dissolution rate abould correlate roughly with in vivo dissolution rate. However, subtle differences exist between the disintegration mechanisms of capsules and tablets. For capsules, at least partial dissolution of the gelatin shell must precede complete dissolution of the enclosed drug. Furthermore, capsule shells generally dis-solve first at the capsule ends, and later at the capsule center. Dablets, on the other hand, disintegrate homogeneously. 65 Thus subtle differences may exist in the in vitrofin viwo dissolution correlation when comparing capsules and tab-

lets. For example, capsules and tablets which exhibit similar in vitro dissolution rates may oahabit subtle differences in in vivo dissolution rate. While such subtle differences may have no theraposulcally significant effect on systemic bioavailability of an orally dosed drug, there are situations in which a significant effect may occur. For example, if a drug has the potential to exhibit an adverse food effect, drug-constaining capaules and tablets which exhibit similar in vitro dissolution rates may actually differ with respect to whether an adverse food effect is observed when the dosage forms are orally desed. In fact, this has been observed for azithro-mycin, as exemplified in the Examples homin.

For the in vitro dissolution mudies disclosed herein, arithmonycin was assayed by HPLC, utilizing a 5 micron alumina based hydrocarbonaceous spherical particle chro-matographic column (15 ccaed).4 cm), and a 5 micros matographic couldmn (1) cascul 4 cm, man a 5 micross abunina hased hydrocarbonaceous spherical particle precolumn (5 cmod) 4 cm) (both available from ES Industries, Marlion, N.J.). A mobile phase consisting of 71% phosphate buffer/29% acetonicile (pH 11) was used, with electrochemical dotection (e.g. Bioanalytical Systems, West Lafayette, Ind., LC-4B amperometric desector with dual series glassy carbon electrodes).

For in vivo food effect studies, acrum azlithromychn is analych using an HPLC assay described by R. M. Shepard et al. (1991) J. Chromatog, Biomed, Appl. 565, 321-337, with amperometric electochemical detection. Alternatively, any saway method that produces equivalent results, for example, bloassay, can be used.

Tablets according to the invention contain, as necessary insticts according to the invention contain, as necessary ingredients, arithromycin and a disintegrant, armorphism of tablet disintegrants are starch, pregriatinized starch, sodium starch glyculate, sodium carboxymethyleellulose, creatinged sodium emboxymethyleellulose (sodium crossulinted sodium emboxymethyleellulose (sodium crossulinted sodium emboxymethyleellulose) carmellose; crosslinked starch available under the registered trademark Ac-Di-Sol from FMC Corp., Philadelphia, Pa.), clays (e.g. magnesism shuminum silicate), relevant station callulose (of the type svailable under the registered trademark Avicel from FMC Corp. or the registered trademark Emocoel from Mendell Corp., Carmel, N.Y.), alginates, guras, surfactanta, effervescent mixtures, hydrotts aluminum silicate, cross-linked polyvinylpytrolidone (svallable com-mercially under the registered trademark PVP-XL from International Specialty Products, Inc.), and others as known in the art. Preferred disintegrants for arithromycin tablets are sodium croacarmeliose (Ac-Di-Sol), sodium starch glycoluse (available commercially under the registered trademarks Principle from Avebe (Union, N.J.) or Generichem, (Linte Falls, N.J.) and Explotab from Mendell Corp.), microcrystalline cellulose (Avinel), and cross-linked polyvinylpyrrolines (EUR-M.). Arithromycin tablets of this investigate. talline cellulose (Avines), and cross-instan polyvimipyrroit-done (PVP-XL). Azithromycin tablets of this investion comprise reithrumycin and 1-25% disintegrant, preferably 3-13% disintegrant based on total tablet weight. For-example, a 4613. for tablet (230 mg activity satthromycin) may contain 9 mg sodium cross-armellose and 27 mg pregelatinized starck

In addition to the active ingredient arithmotycin and a disintegrant, tablets according to this invention may be formulated to optionally include a variety of conventional excipients, depending on the cract formulation, such as binders, flavorings, buffers, diluents, colors, lubricants, awestening agents, thickening agents, and gildants. Some excipients can serve multiple functions, for example as both binder and disintegrant.

Examples of binders are acacia, cellulose derivatives (such as methylceliulose and carboxymethylceliulose, hydroxypropylmethylcelluloss. hydroxypropylcollulose. hydroxyethylcellulose), gelatin, glacose, dextrose, xylltol, polymethacrylases, polyvinyhymolidone, starch paste, sucroso, sorbitol, pregelatinized starch, gum tragacanth. alginic acids and salts thereof such as sudium alginute, magnesium aluminum silicate, polychylene glycoi, quar gum, bentonites, and the like. A preferred binder for azithromycin tablets is pregelatinized starch (available, for example, under the registered trademark Starch 1500, from Colorcon, Inc., West Puint, Pa.).

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants leaves, flowers, fruits, and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreso, peppermint oils, clove oil, bay oil, anise oil, excalyptus, thyme oil, cedar leaf oil, oil of natureg, oil of sage, oil of bitter almonds, and cassia oil. Also useful as flavors are vanilla, clous oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, orange, grape, lime and grapefruit, and fruit essences, orange, grape, depend on a number of factors including the organoleptic effect desired. Generally the flavoring will be present in an amount of frum 0.5 to about 3.0 percent hy weight based on the total tablet weight, when a flavor is trans-

A variety of materials may be used as filters or diluents. Examples are spray-dried or anhydrous lactuse, sucrose, destrouc, mannial, sorbital, starch (e.g., starch 1500), cellulose (a.g. microcrystalline cellulose; Avicel), dihydrated or anhydrous dibasic calcium phosphate (available commercially under the registered trademark Emcomptess from Mendell or A-Tab and Di-Tab from Rhone-Poulenc, Inc., Mommouth Junction, N.J.), calcium embouate, calcium sulfate, and others as known in the ar.

Lubricanta can also be employed herein in the manefacture of certain dosage forms, and will usually be employed
when producing tablets. Examples of lubricants are magneslum stearate, stearie acid, glyccrylbehaptate, polyethylene
glycol, ethylene oxide polymers (for example, available
under the registered trademark Carbowax from Union Carbide, Inc., Danbury, Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl furnarate,
DL-leucine, colloidal silles, and others as known in the art.
Preferred lubricants are magnesium attentate, and mistures of
magnesium stearate with sodium lauryl sulfate. Lubricants
generally comprise 0.5 to 7.0% of the total tablet weight.

Other excipients such as glidants and coloring agents may also be added to azithromycin tablets. Coloring agents may include titantum dioxide and/or dyes subable for food such as those known as F. D. & C. dyes and natural coloring agents such as grape akin extract, beet red powder, bets carotene, annato, carmine, harmetic, paprike, and so forth. A coloring agent is an optional ingredient in the compositions of this invention, but when used will generally be present in an amount up to about 3.5 percent based on the total tablet weight.

As known in the art, tablet blends may be dry-granulated or wet granulated before tableting. Atternatively, tablet blends may be directly compressed. The choice of processing approach depends upon the properties of the drug and chosen excipients, for example particle size, blending compatibility, density and flowability. For azithromycin tablets, granulation is preferred, with wet granulation being most preferred. Azithromycin may be wet-granulated, and then other excipients may be asked axitagranularly. Atternatively, azithromycin and one or more excipients may be wet-granulated. In addition, tablets may also be coated, with a coating that exhibits little or no effect on or interference with tablet dissolution, to assure case of swallowing or to provide an elegant appearance.

In a preferred embodiment, tablets of this invention are 63 film-coated to provide case of swallowing and an elegant appearance, Many polymeric film-coating materials are

known in the art. A preferred film-coaling material is hydroxypropylosethylecillulose (HPMC). HPMC may be obtained commercially, for example from Colorson Corp., in coaling formulation a containing excipients which scare as coaling aids, under the registered trademark Opadry. Opadry formulations may contain lacture, polydextrase, triacetin, polyethyleneglycol, polysorbate 80, titanium dioxida, and one or more dyis or lakes. Other adiable film-forming polymers also may be used herein, including, hydroxypropyleniulose, and any late-methacrylate copolymers.

The tableting process itself is otherwise standard and readily practiced by forming a tablet from a desired blend or mixture of ingredients into the appropriate thepe using a conventional tablet prous. Tablet formulation and conventional processing techniques have been widely described, for Example in Pharmaceutical Dosage Forms: Tablets: Edited by Lieberman, Lachman, and Schwartz; Published by Mancel Dekker, Inc., 2d Edition, Copyright 1989, the text of which is herein incorporated by reference.

The azithromycin closuse forms of this invention also include powders to make oral suspensions, and also the oral suspensions, and also the oral suspensions themselves. Generally the powder is a non-taking, free flowing powder which is sold direct to pharmacies or other retail outlets and then made up into the actual suspension by a pharmacist. The oral suspension is thus the actual desage form ingested by patients. The typical shelf life for a suspension is about five days because azithromycin therapy is generally of five days duration.

Azithtomycin suspensions according to the invention contain, as accessary ingredients in addition to azithrumycin, one or more thickerning agents in a total amount of 0.1 to 2%, and a buffer or pH-akering agent is an amount of 0.1 to 2.5%, with percentages being based on the weight of the dry powder formulation. Dispersing agents may also be used in an amount of from 0.05 to 2%. Preservatives may also be used is an amount from 0.1 to 2%.

Sultable thickening agents function as suspending agents and include, for examples, hydrocolitoid gams known for such purpose, examples of which include anothen gam, guar gum, tocast bean gam, guar tragacenth, and the like. Alternatively, synthetic suspending agents may be used such as solium carboxymethy keellulose, polyvinylpytrolidone, hydroxymropylcellulose and the like.

Dispession accounted.

Dispersing agents include colloidal silicon dioxide, available from Caber Corporation, Boston, Mass. under the trade designation Cab-O-Sil.

For the purpose of preparing formulations of a powder for oral suspension, the bitter taste of azithromycin may be masted by including a basic buffer or pll-shering agent which will provide a pH of approximately 10 in the constituted suspension. Maintensace of the pH at around 10 minimizes the quantity of azithromycin in solution, and thus masts the bitter taste of the drug. Many combinations of flavors or flavor systems may be used in addition to mast the bitter taste of azithromycin. Preferred flavors are those which provide a constant flavor for approximately 5 days at the elevated pH of the formulation after constitution. A preferred flavor system consists of spray dried cherry #11929, #nitical creme de vanilla #11489, and apray-dried artificial banena #15223 available commercially from Bush Boake Allen, Irc., Chicago, IR. Artificial awesteners may take he used.

A powder used to make a suspension berein may also contain conventional optional ingredients such as (1) wet-ing agents such as norbitan monolaurate, polysorbate 80, and sodium fauryl sulfate; (2) anti-fourning agents and (3) sweeteners and filters such as glucose. The powder may also creating a buffer to maintain a high pH upon reconstitution, as discussed above. Sultable buffers and pH-altering agents

include anhydrous tribusia sodium phosphate, anhydrous sodium carbonate, glycind, and the like. Suitable preservatives are well known, for example sodium benzoate and like like. After swallowing, azithromycin from a suspension dissolves quickly.

In the preparation of azithroniycin powder for oral suspension formulations, all ingredients may be blended together and deagformerated, as known in the art. Preferably, azithromycin and flavors are blended, and other ingredients are separately blended. Finally, these two blends are blended and deagglomerated.

Preferred oral suspensions are those which resuspend easily after constitution with aqueous media and which do not cake on storage after constitution. Preferred suspensions contain sucrose NP, when sucrose is used, and anhydrous exciptents when available, to assure facile suspension upon constitution. The drug-containing powder is generally reconstituted with water.

Suspensions of this invention exhibit about 90% dissolution of azithromycia in vitro in about 15 minutes. The test can be summarized as follows:

Shake the azithromycin-containing bottle to luosen the powder, and constitute the sample as per label instructions, e.g. as described in Example 12 to provide a 40 mg/ml azithromycin suspension. Shake the bottle vigurously for 2 minutes, then allow the bottle to sit for 30 minutes. Shake 25 again vigorously for 15 seconds. Withdraw 5 ml from the bottle (typically equivalent to 200 mg of axistromycin), taking care to eliminate air bubbles. Carefully dispense the 5 ml aliquot of the azishromycin suspension approximately 10 cm over the surface of the dissolution medium (0.10M 30 addium phosphase buffer, pll 6.0) in a USP Apparatus 2, with the paddles positioned 2.5 cm from the bottom of the vessels. Begin rotating the paddles at 25 rpm, after the Oral Suspension samples have sunk to the bottom of the vessels. Remove approximately 10 ml from the dissolution vessel at each sampling time, filter, and assay filtrate for azithromycin using the 11FLC assay described previously.

An azishromycin unit dose packet dosage form (also referred to berein as a "sachet") consists of a unit packet, designed to be emptied into an aqueous vehicle, for example water or a natural or artificial fult beverage. The packet contains a blend of azishromycin and excipients which is thus seconstituted. The packet contains, as necessary ingredients, azishromycin and a dispersing agent which makes the sachet powder free flowing, for example colloidat silicon dioxide such as Cab-O-Sil from Cabot. Generally the dispersing agent such as Cab-O-Sil from Cabot. Generally the dispersing agent is present in an amount of about 0.2 to 2.0 by weight based on the weight of the dry sachet as it is to be sold. The dispersing agent also serves as a glidant. The formulation may also optionally contain ingredients including (1) a filler or avectener (e.g. glucone); (2) a buffer (e.g. softium phosphate); (3) a weiting agent such as a surfactant, for example sodium larryt sulfate, and (4) flavort such as any of those enumerated herein, and the like. The powder in the packet flows freely and disperses quickly, essentially immediately upon stirring when reconstituted. Azithromycin unit dose packet dosage forms may be prepared by blending and deagglomerating all ingredients, as known in the art. Preferably, the filler (e.g. sacruse), buffer (e.g. anhydrous tribasic sodium phosphate), and glidant (e.g. colloidal silicom dioxide) are blended and deagglomerated, followed by blending with azithromycin and flavors, followed by deagglomeration. The azithromycin in the packet dissolves quickly when evaluated as follows. The contents of a packet are added to a 250 ml heaker containing 60 ml water treated with the Milli-Q Plus system, Millipore Corp. (>18 megohms resistivity). The contents of the beaker are stirred with a spoon until a hornogeneous suspension is obtained (1–2 min.). With the paddles raised, the suspension is poured into

10

the center of a dissolution vessel of a USP-2 dissolution apparatus containing 900 mt 0.1M sodium phosphate buffer, pli 6.0. The paddles are then lowered into the vessel, and rotation is began at 50 pm. 10 mt. aliquous are removed at each time point, filtered, and filtrates are assayed for azithromycin in solution, using an HPLC assay as described above. Using this method, greater than 90% dissolution of a 1 gm azithromycin packet is observed in less than 5 minutos. The packet that does not exhibit an adverse food effect.

As stated, the oral azithromycin dosage forms disclosed and described above can be administered to a mammal, including man, in need of such treatment when the mammal has eaten, regardless of how recently and of the nature and quantity of food, without exhibiting an adverse food effect. To this end, and as an additional feature of the invention, this invention provides a therapeutle package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said package, written (i.e., printed) matter mon-limited as to whether the dosage form can be taken with or without food. The written matter is of the type containing information and/or instructions for the physician, plumacial or patient. The written material can be "non-limited as to whether the dosage form can be taken with or without food" by virtue of including no statement regarding whether or not the dosage form can be taken with or without food, i.e. the statement is silent with regard to food affects. Alternatively, the written material can be non-limited by containing one or more statements affirmatively informing the user (i.e., the patient, pharmacial, or physician) that the said oral dosage form can be taken by or administered to a patient regardless of whether the patient has caten or otherwise imbibed food (optionally, for example, also stating something like "without regard to type or quantity of food"). The written material can not contain limiting language with respect to food, e.g. "This dosage form can on the taken with food" or "This dosage form can on the taken with food" or "This dosage form can be given after the patient has fasted" or the like.

The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-scalable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual dosages for pressing out of the pack according to a therapoutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a hiquid suspension. It is leasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

Printed or otherwise written matter is associated with the package in which the arithromycin dosage form is sold. The term "associated with" is intended to include all manners in which written matter, such as instructional or informational materials can be associated with a medicament, as known conventionally in the art. Thus written matter can be associated with the container, for example, by being: written on a label (e.g., the prescription label or a separate label) athestively affixed to a bottle containing an azithromycin auspension; included inside a container as a written package insert, such as inside a box which comains unit dose packets; applied directly in the container such as being printed on the wall of a box; or attached as by being tied or taped, for example as an instructional card affixed to the neck of a boule via a string, cord or other line, lanyard or tether type device. The written matter may be printed directly on a unit dose pack or blister pack or blister card. If the written matter attirmatively contains a non-limiting assempest, the written

11

matter may contain other information in addition. An affirmative non-limiting statement may, for example, read like the following exemplary statement:

This product does not exhibit an adverse food effect and may accordingly be administered to patients whether or not they have eaten and without regard to type or quantity of food.

quantity of food.
or something similar, such as "may be taken without regard
to food".

The invention will now be illustrated by the following examples which are not to be taken as limiting. In general, the examples demonstrate that (1) arithromycin capsules exhibit an adverse food offset, and that more slowly dissolving capsules exhibit a larger food effect, and (2) azithromycin fast dissolving tablet, powder for oral suspension, and unit does packet dosage forms do not exhibit an adverse food 15 effect.

EXAMPLE 1

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin 20 doted in a capsule dosage form with moderate dissolution

Capaules were prepared which contained 250 mg activity arithromycja. The formula for these capaules is presented in Table 1. The dissolution behavior of these capaules was 25 evaluated by the method previously discussed, using rotating paddles, 100 rpm, 900 rml p11 6.0 phosphate buffer at 37 degrees C. The average % azithromycin dissolved at 15 minutes was 25%, and at 30 minutes was 76%.

The effect of feeding on asthromyoin bioavailability was determined as follows. Eleven healthy male human volunteers were orally desed with 500 mg astithromyoin (2×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were desed after an overnight fast (food and fluit) of 12 hr. The done was awallowed with 150 ml water, and a further 150 ml water was taken at 1 hr post-tosing. On the other occasion, the subjects consumed a neal consisting of milk, bread and butter, bacon, 2 fried eggs, and coffee. The dose was administered with 150 ml water within 30 minutes of cumpletion of the meal, Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr pust-dosing. Serum atthromyoin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition. The mile 45 AUC/fed/AUC/fasted was used as a measure of the effect of food on oral bioavailability. The average AUC/fed/AUC-fasted was 0.22, with lower and upper 90% confidence levels of 0.06 and 0.84, respectively.

TABLE

Formulation of 250 mg Azithromycla C white optapes locking type	
ENGREDIEN!	MG/CAPSULE
Azitheromycia*	263.72
Luciote, ashydrous	149.88
Corn suech, hydrous	47.0
Magnesium stearnes/Sodiace Impyl nations (90/10)	9.40
TOTAL	470.0

^{*}Hated on a bulk putercy of \$4.5%; Non-stolchiometric hydrac.

EXAMPLE 2

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin

12

dozest in a capsule dosage form which dissolved more quickly than the capsules of Example 1.

Azithromycia espaules (250 mg strength) were prepared according to the furmula in Table II. Dissolution of azithromycin from these captules was evaluated as in Example 1. In 15 minutes, 97% of the encapsulated azithromycin was dissolved.

The effect of feeding on azildromycin bioavailability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg azildromycin (2×150 mg capaties), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed fried in one tablespour botter, two strips of bacon, two ounces of ham, two pieces of tossi with two testpoons of butter and two pats of jelly, and eight ounces whole far milk. The orat doses were administered with 250 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azilmonycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug acrum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfet/AUCfested was used as a measure of the officer of food on arithromycin oral bloavailability. The average AUCfet/AUCfested was 0.80, with lower and upper 90% confidence lovels of 0.67 and 0.96, respectively.

TABLE D

Formula for Azishvogycin capsulet. This formula was prepared as a day granulation and was founded into 60 opaque locking

PACINEDIENT	MORCAPSULE	
Asithomycla Dibydesc*	262.05	
Lacture, anti-prirous	191.33	
Corn stanth, hydrons	47,00	
Magazetun sirana-Sadium	7.10	
lough sulfate		
TOTAL	470.00	

^{*}Equivalent to 230 mg arithmotycle, beard on a bulk passacy of 95.4%.

EXAMPLE 3

This example is comparative and demonstrates the effect of a light breakfast on systemic exposure of szithmenyein dused in a capsule desage form which dissolves quickly.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycin from these capsules was evaluated as in Example 1. In 15 minutes, 99% of the encapsulated azithromycin was dissolved.

The effect of a light (Conlinents)) breakfast on azithromycin bioweilability from this desage form was determined as follows. Twelve healthy male human volunteza were orally dosed with 1000 mg azithromycin (4x250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed after consumption of a light breakfast consisting of two rolls with batter and jam and Ca. 300 mi of coffice or tea with milk. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dusing, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 46.5 hr post-dusing. Scrum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the

13

area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCled/AUClasted was used as a measure of the effect of food on oral bioavailability. The average AUCled/AUClasted was 0.71, with lower and upper 90%: s confidence levels of 0.53 and 0.95, respectively.

EXAMPLE 4

This example demonstrates the effect of a high fat break- 10 fast on systemic exposure of azithromycin dosed in a tablet desage form which dissolves quickly.

Azithromycin tablets were prepared according to the formula given in Table III. Dissolution evaluation was carried out as in Example 1. At 30 minutes, 100% of the 13 azithromycin was dissolved.

The effect of feeding of azithromycin bioavailability from these tablets was determined as follows. Twelve healthy made human vohanteers were orally dosed with 500 mg azithromycin (2x250 mg tablets), on each of 2 occasions, On 20 one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after consumption of a meat consisting of two ages fried in one tablespoon butter, two strips of bacon, two pieces of mast with two teaspoons of butter and two pass of jelly, eight ounces whole-fat milk, and 6 ounces hast-brown potatocs, ingested over a twenty minute period. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 for post-dusing. Serum azithromyclin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug scrum concentration vertice.

The ratio AllCred/AUclasted was used as a measure of ³⁵ the effect of food on trial bioavailability. The average AUClcd/AUClasted was 0.97, with lower and upper 90% confidence levels of 0.82 and 1.13, respectively.

TABLE III

Formula for anthromycis film count tables. This formula was congressed to form a 0.263" is 0.5312" modified expanies, upper engrated "Piler", hower toment, tablet, and was content with "pink Opady".

INGREDUAY	WEXHIT (MG/UNTT)			
Anthomycus dubydrau?	267.05			
Preprintment surch**	27.00			
Calcium phosphete dibasie, aubydrous	13E B4			
Sodium emsemmellose***	9.00			
Magnesium etemas Sudiem Lauri militis (SIV)	11.11			
Pick Opedry 1744	18.00			

^{*}Equivalent to 250 mg artiformycia; based on a bulk potency of 95.4%.

EXAMPLE 5

This example demonstrates the effect of a Japanese meal on systemic exposure of azilthromycin dosed in a tables dosage form which dissolves quickly.

A tablet dusage form of azithromycin was prepared according to the formula described in Table 1V. Dissolution 65 of this dusage form was evaluated as in Example 1, in 15 minutes, 100% of the azithromycin duse was dissolved.

14

The effect of feeding on azishromycin bioavallability from these tablets was determined as follows. Eight healthy male human volunteers were enally dosed with 500 mg azishromycin (2×250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed 30 minutes after consumption of a Japanese meal cursisting of rice, miso coup, fried egg, seaweed, apinach, and pickles. The oral doses were administered with 200 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 hr post-dosting. Serum azishromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeling condition.

The ratio AllCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.00, with lower and upper 90% confidence levels of 0.87 and 1.15, respectively.

TABLE IV

Azithorsycin fits-consid tablet formula. Capeuter plan white film-conind lables (0.262° nr 0.5312") were compressed and then conted with "White Opadry" and "Clear Opadry".

INCRUDIENT	WEIGHT (MG/TABLET)		
Arithromycis dikydose*	262.05		
hugelminised starther	27.00		
Calcium phosphate dibasic. Athrohum	139.84		
Nuclium croscerosilosca**	9.00		
White Opadry ##	12.125		
Clear Openhyses	0.675		
Magnesium Stearges	13.11		
Sodium Lauryl Salfate	·		
(90/10)			

^{*}Equivalent to 250 mg arithmospeia, based on a bulk potency of 95.4%, **Sureh 1500.
**Sureh 1500.
**An-15-Sol

EXAMPLE 6

This example compares the effects of a high fat breakfast and a low fat breakfast on systemic exposure of szithromycin dosed in a "Powder for Oral Suspension" desage form.

An azithromycin "Powder for Oral Suspension" was prepared according to the formula in Table V. This formula was designed to wet and disperse quickly when reconstituted with an equeous vehicle. Dissolution of this suspension was ovaluated as described in the "Detailed Description". In 15 mlautes 97% of the azithromycin dose dissolved; in 30 minutes 99.6% of the azithromycin dose dissolved.

The effect of a high fat meal and a low fat meal on azithromycin bioavailability from thit auspension desage form was determined as follows. Six healthy male human volunteers were orally dosed with 500 mg azithromycin (12.5 ml of a 40 mg/ml oral auspension), on each of 3 occasions. On one excasion, the subjects were dosed after an overnight fast of 10-12 hr. On another occasions the subjects were dosed after consumption of a high fat meal consisting of two eggs fried in one tablespoon butier, two strips of bacon, two pieces of tosst with two pass of butter, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. On the third occasion, the subjects were dosed after consumption of a low fat meal consisting of one ounce of Cheerius (registered trademark of

^{***}Ac-Di-Sol.

^{##}Contains lactore, hydroxygropy) mesbylecitatore, triaxiom dioxide, triacetin, and D&C Red No. 30 Abstracting Lake.

21

14

General Mills Inc.) cereal and eight ounces of whole mills. The oral doses were administered with 240 ml water (two 60 ml rises of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Sorum azithromyelin concentration was determined using a high performance liquid chromatography assay. For cuch subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCled/AUClasted was used as a measure of the effect of food on oral bloavailability. For the high fat meal, the average AUCled/AUClasted was 1.01, with lower and upper 90% confidence levels of 0.79 and 1.28, respectively. For the low fat meal, the average AUCled/AUClasted was 1.04, with lower and upper 90% confidence levels of 0.82 and 1.33, respectively.

TABLE V

Formula for azithromycle "Powder (or Chal Suspension". To reconstitute this formulation, 0.52 ml water was added per gen dry formulation.		
NOREDIENT	WEIGHT (MG/BOTTLE)	
Azishromycin dilhydrate*	838.57	
Sucrose	15487 74	2
Sodiera phosphate albasic, autyrkosi	70.01	
llythosypupyleidhikus (Klucel- EF)	26 62	
Xamthan gum (Kalicol)	26.62	
FDAC RE4 #40	0.67	3
Spray Dried Cherry #11529	59.94	
Art. Crame de Vasilie #11489	133,76	
S.D. Art. Hamena #15223	99.96	
TOTAL	16743.41	

[&]quot;Based on a bulk potency of 95,4%.

EXAMPLE 7

This example demonstrates the effect of a high fat break- 40 fast on systemic exposure of azithromycin dosed in a "Single Dose Packet" (suchet) dosage form.

A "Single Doss Packer" (suchet) dosage form of azithroinycin was prepared according to the formula described in Table VI. Dissolution of this dosage form was evaluated as 45 described in the "Destilled Description" above. In 15 nunutes, 99% of the azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from this aschet dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (1 gm sachet), on each of 2 occasions. On

16

one occasion, the subjects were dosed after an overnight has of at least 12 hr, and on the other occasion the subjects were dosed after consumption of a high-fat meal consisting of baced occasion from the property of the subjects were dosed after consumption of a high-fat meal consisting of baced, we pieces of toast with two teaspoons of butter and with two pats of jelly, eight ounces whole-fat milk, and 6 ounces hash-brown potages. The oral doses were administered with 240 ml water (two 60 ml risses of the oral syrioge plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.25, (1.5, 1. 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, and 120 hr post-dosing. Scrum arithromyclin concentration was determined using a high performance liquid chromaingraphy assay. Fir each subject under each dusing condition, the area under the drug scrum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.12, with lower and upper 90% confidence levels of 0.99 and 1.27.

TABLE VI

Formula for antihremycis "Unit Dose Packet" dosage form. This blead was propiered, and filled into 3.25" x 4" white paper alumnum/polyethylene laminate suchess. To reconstitute for dosing, the contents of a sucher is added to 60 and water, and attend well.

	INGREDIENT	WEIGHT (GMAUNTI)
	Azijinonyoja dikydrate*	1.041
10	Sucrose	9,707
	Sodium photohers primer, anhydrous	0.088
	Colloidal silicoo dioxide	0.055
	Sprey (Xied at themy #11929	0.034
	Spray Dried att banna #15223	0.064
ÍS	TOTAL.	11.000

^{*}Equivalent to 1 gm anthromycin, based on a bulk potency of 95.4% for anthromycin dibydraus.

EXAMPLE 8

Azithromyclo tablets of this invention were prepared at 150, 200, 250, 300, 500, and 600 mg dotage strengths. Tablet cores were prepared by wet granulation of all tablet core ingredients (except magnesium steamer/sodium laury) tulfate. The dried granules were blanded with the lubricans mixture magnesium stearate/sodium laury) sulfate, followed by tableting on a tablet press. Tablets were coased with an aqueous film oual comprising colored and/or clear Opadry. These tablet formulations do not exhibit an adverse food effect. Tablet formulations were as described in Table VII.

TABLE VII

	WEIGHT (MGTABLET)					
Componer	150 MG STRENGTH	200 MG STRENGTH	250 MG STRENGTH	300 MG STRENOTH	SOC MO STRENGTH	600 MG Strength
Azido emycia dihydrate	157.23	209 613	762.05	314.66	524.10	628.93
Pregelatinized Stanh ^{où}	16.20	21.60	27.00	32.40	54.00	64.80
Calclum photohute tihanic, anhydrous	#J.3IE	EJE Ö1	136.04	156.61	277.68	333.2)
Sodime crescurock	5.400	7.200	900	10.80	12.00	21.60

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60

17

TABLE VII-continued

	Lisamples of acidin	myan ublet for	outsions which	do pot czajbij a i	food effect.	
	WEIGHT (MO/TABLET)					
Component	ISO MG STRENGTIK	1200 MG HTGN/JKT2	250 MG STRENGTH	300 MG STHENGTH	300 MG Strength	800 MG
Magnesion steamed Sodies buryl sulless	7.865	10.466	13 11	15.73	26.22	31.46
(90/10) Opadry @	g.1	101	135	16.2	27.0	72.4
TOTAL	274.1	370 8	463.5	556.2	927.0	1,1124

EXAMPLE 9

Additional tablet formulations of azithromycin (250 mg) are prepared which do not exhibit an adverse fond effect and are described to Table VIII. The diluent in these formulations (calcium phosphato dibasic, anhydrous) may be subatituted by calcium phosphate dibasic dihydrate, microcrys- 25 tailine cellulose, factore NF/BP/EP/IP, or other appropriate diluent. The lubricant in these tablets (magnesium stearaus) sodium lauryl sulfate, 90/10) may be substituted by magnestum stempte and/or colloidal silica or sodium steary) furnistate. Magnesium stearate and sodium steary) furnarate are generally used in amounts constituting 0.5-7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1 1% of the total tablet weight. While considerable laduate in relative excipient ratios is possible. the calcium phosphate/progelatinized starcts ratio should be around 2:1 or greater. The Opadry film coat is not necessary to achieve food-independent drug exposure, but serves to Improve ease-of-swallowing and tablet appearance and serves to differentiate strengths. The Opadry cost may comprise between 2-6% of the total tablet weight. Tablets at other potencies may be obtained by maintaining the approxithate azinhromycin/excipient ratios described in Table VIII. and increasing or decreasing total tablet weight.

TABLE VIII

Examples of unichromycis tables formulations (250 mg) which do
not exhibit an adverse load affect.

	WE	CHT (MO/TAB)	ראַ.
COMPONENT	FURMU- LATION 1	FORMU- LATION 2	PORMU- LATION 3
Azidronycia dilydria	362.05	262.05	262.01
Propelationsed	50.0	13.9	50.0
Calcium phosphets obtain ank	117.84	140,94	104.B4
Sodium creteatreliese	9.0	20,0	20.0
Magnesium Monachodium	13,51	13.}1	13.11
lacryi salfase Opadry W	13.50	13.50	13.50
TOTAL.	463.5	463.5	463.5

Chydraxypropylanudylcellulose and appropriate phasicizers, film-coaring lers, and lares

EXAMPLE 10

18

Further 250 mg azithromycia tablet formulations are prepared which do not exhibit an adverse food effect and are presented in Tubles IX and X. In these formulations, maize starch, sodium starch glycolate, and crosslinked polyvinylpyrrolidone serve as disintegrants. Calcium phosphato dibasic, lactose NF/BP/UP, and microcrystalline cellulose scree us diluents.

Magnesium stemale/sodium lauryl sulfate serves as a lubricani. Magnesium steurase/sodium lauryl sulfate may be substituted by magnesium stearate and/or colloidal silica or sodium stearyl (unuxuse. Magnesium stearate and sodium sodium stearyl furnarate. Magnesium stearste and sodium stearyl furnarate are generally used in amounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an unount constituting 0.1–1% of the total tablet weight. While considerable latitude in relative exciptent ratios is possible, the dittent/disintegrant ratio should be around 2:1 or greater. The Opadry film cost in not necessary to archiver food-independent drug exposure, but serves to improve case-ut-awallowing and tablet appearance. The Opadry cost may comprise between 2–6% of the total tablet weight. Tablets at other potencies are obtained by maintaining the approximate azithromycindexciptent ratios described in Tablet 1X and X, and increasing or decreasing total tablet weight. These formulas are illustrative, and substitutions of other disintegrants, diluents, and lubricants are possible, as other disintegrants, diluents, and lubricants are possible, as known in the art.

TABLE IX

azithronycin lablet formulations which do not nabilik an adverse lood effect.				
	WE	WEIGHT GARGITABLETT		
OMPONENT	PORMU- LATION 4	PORMU- LATION 3	-UMKOR 1 MOTALI	
zijkronyciu ibyczęści	262.05	267.03	262.05	
taine surch	139	27.0	\$9.0	
alciem hosphate, lbasic** OR	153.94	130.64	115.84	

lacture NV/NP/EPVIP (AR Migrarystations cellulos: counters Society stands glycolate# OR Createster! 9.0 90 9.0 polyvku lpyrodi dana VII

^{*}Band on a theoretical potancy of \$5.4%,

**Starch 1500.

Reg. Ac-Di-Sol.

Willydroxypropylmethylcelluluse and approhylocilekuse and appropriate plusticises. Sim-centrag adjuvents, opacifier, and lakes.

19

TABLE IX-continued

	. WE	CIT (MC/TAB	டிற	•
COMPONENT	FORMU- LATION 4	FORUMU LATION 5	FORMU-	
Magnesiam stearste/sodium leary) salfate	13.11	13.11	13.11	!
Opedry @	13.5	13.5	13.5	
TOTAL	463.5	467.5	463.5	

15 particularities to 250 mg atthnostycin.

*Alto called starch NP or consistent

*Either resiptions or sillydrate

Reg. Explosab or Principl

**Reg. Explosab or

TABLE X

as adverse (and office		
W.F.	igit). (MCA1VBI	LED
14)AMU- LAITON 7	HOHMU- LATION B	FORMIS LATION 9
	WEI	MFIGHT, (MOLVER)

	Wh	IGILL (YACAZYB)	LED	-
COMPINENT:	IV)AMU- 7 NOTEAL	NONMU- LATION S	FORMI LATION 9	
Authorayain dilwinact	262 05	262.05	262.05	30
Maise starch* Calcium phosphain, dibasic** OR	13.9 140.94	27.0 144.84	27 0 127.84	
Laceme NWBP/EP/IP OR Microsystation collulose				35
Sodium starch glycolano UR Crosslickol polywinylpymali- doness	200) ,	20.0	40
Magazalam steaste/polium lawyl salfate	13.11	13.11	13.11	
Opadry #	115	13.5	13.5	45
TOTAL	461.5	463.5	463.5	

"Also called starch NF or comsumes
"Either subphress ar dilydease
Reg. Exploits for Primojel
Neg. PVP-RL from International Specialty Products Inc.
##Hydroxypropylographylathless and appropriate pissistic
adjuvenes, opending, and labor.
#Equivalent to 250 tog anithromycin.

EXAMPLE 11

The "Powder for Ond Suspension" formulation described in Table XI was prepared. This formulation does not exhibit $_{80}$ an adverse food effect.

20

TABLE XI

A formulation for unithrungein "Pureder for Oral Suspe-	
CORITINIA)	WEIGHT (MG/GM)
Azidanmycin dihydrate	47 97
Sucrose NI:	579.71
Soridus, crystallise, powder, NF/PCC	249.86
Sodium carbonne, anti-drova, NF	18.04
Sociore bereaue, M-7-CC	435
Transcenth eura powder, NF	14.49
Trustrum diesals LISP	14,49
(bilakia) alicos aleadár, NY	1 45
Aminuacetic acid (glycine) USP	5.00
Spray-dried Art. Strawherry #22653	15.74
Tropical apple punch #26508	7.63
Spray-thred peoperment attch #15634	0.15
TOTAL.	1000.00

EXAMPLE 12

EXAMPLE 12

Azithromycin "Fowder for Oral Suspension" formulations are prepared as illustrated in Tables XII and XIII. The unit potency of these formulations is 600 mg azithromycin/boille, and the use potency after constitution with water is 40 mg/ml. To constitute, 0.52 ml water is added per gm of blend, 9 ml. water and 16.74 gm blend produce approximately 20 ml suspension. These formulations toclude 200 mg Azithromycin/bottle overfill. The listed "flavor system" may be freely substituted with other flavors which provide a pleasant taste and are stable at pH 10 over the shelf-life of the constituted suspension (approximately 5 days). The dye may also be freely substituted. The formulations in this lixangle are illustrative, and not limiting. These formulations to not exhibit an adverse food effect.

TABLE XII

timesples of for	rmulenome of Arisi Suspensio		er for Cirol
	WEIGHT (MO/BOTTLE		
COMPONENT	POMMU- LATION I	FORMU- LATION 2	FORMU- LATION 3
Azithrusyciu dihydrate	238.57	838.57	131.37
Secrute NF	15487.74	15370.54	15417.74
Sodium phosphata Inhanic anhydrous	70.01	70.01	70.01
llydrusypropyl- rellulose	26.67	26.43	9
Xeidpiro Rum	26.62	24.42	٠,
Sodium carboxy- reshylophalose	O	0	53.24
Catholdal silicon Goside	0	16,74	0
Ulycine	0	100,46	0
Epray-dried charry #11929		59,94	
Art. Creme de Vanilla #11489	133.28	133.28	133.28
Spray-dried Art. Banana #15223	99.96	99.96	99.96
FD&C Red #40	0,67	0.67	0.67
TOTAL.	14743.41	16743.41	16743.41

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	IVARIE	X111		_	
Examples of formeladoes of Audeomycis "Powder for Unil Suspensive"					
	W	исивот	TLE	- ` `	
COMPONENT	HORMU- LATION 4	FORMU- LATION 5	FORML- LATION 6		
Azidzonycia ńlkydzak	838 57	83E 57	#3K.57	10	
Sucresc NF	15138.55	7743.87 7743.87	7656.37 7656.37		
Sudhun carbonne, mbydrous, NP	307 00	ō	150 00		
Sodium phosphale vibuse anhydrous	O	70,01	35,00	15	
Hydroxypropyl- callulate	0	26,62	17 75		
Newhen gare	0	26.62	1775		
Sodium enticky- menylechniese	53.24	Q	17,75		
Colloidal allicon dioxide	1674	0	10.00	20	
Glyclor	100.46	0	30.00		
Spray-dried charry #11929	19.94	19.94	59.54		
Art. Corme de Vandilla di 1419	133.28	133.28	133.26	25	
Spray-dried Art. Banana #15723	99.95	99,98	99,96		
FDAC Red HO	0.61	0.67	0 67		

EXAMPLE 14

16743 41

16743 41

16743.41

TOTAL

The following fermulations of unit dose packets of azithromycias are prepared as being exemplary, not limiting, of the invention (Tables XIV and XV). The flavor system for these dosage forms may be freely substituted with any flavor system which provides a pleasant taste when the contents of 40 the packet are reconstituted in water or an aqueous heverage. When constituted in water or an aqueous beverage, these dosage forms do not exhibit an adverse food effect.

TABLE XIV

Examples of unit dose packet formulations.				
CUMINOSITION	PORMI) LATION I	FURMU- LATION 2	JORNU- LATION 3	
Authoromycla dibydraie	1.04	1.04\$	1.012	
BACTORS	9,707	9,707	5.0	
	0	٥	0	
phosphare phosphare mindeum	αÒ	0.2	0.084	
andium carbonae, sahyaran	0	0	0	
g)yeine	0	٥	o	1
colloidal nilicon Genida	0.071	0.22	0.055	
Spay-dried at. charry #11929	0.034	0,034	0.058	
Spray dried #1.	0.064	0,064	0.064	
#15223				

TABLE XV

Evan	ples of windows pe	eke formulation	<u>. </u>
COMPOSITION	FORMU- LATION I	FORMU- LATION 2	POTUMU LATION !
Azithromyciu drhydrate	1.048	1,044	1.048
SUCTURE	o	4.85	415
scrbital	9 707	4.65	485
รงตับอา	0.048	0.068	0.044
bywiste hipary:			
eorphysicone Tryphysicone	0	0	0.022
carbunaic, enbydrous			
glyclas	0	0	Q 022
cultuidal d'Écon Bioxide	0 053	0.055	0.055
Spray-dried art. Cherry #11929	0.038	0.034	0.038
Spray dried art. beinna #15223	0 064	0.064	0.064

What is claimed is: '

I. Au and dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as act forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ral sodium phosphate buffer pli 6.0, 37° C., with paddles turning at 100 pm, provided that said closage form contains less than a taue-masking amount of an alkaline earth metal oxide or hydroxide.

2. A desige form as defined in claim 1, wherein said mammal is a human.

3. A dosage form as defined in claim 1, further comprising

a flavoring agent.

4. An oral dosage form of azishromycin which is in the form of a powder for oral suspension containing anhydrous buffer, which is administrable to a mammal that has eaten, swhich comprises azishromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits not adverse food effect, said dosage form effecting at least about 90% dissolution of azishromycin within about 30 minutes when an amount of the durage form equivalent to 200 mg of azishromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 pm, provided that said dosage form contains less that a taste-masking amount of an glasine earth metal oxide or hydroxide.

5. A dosage form as defined in claim 4, wherein said mammal is a human.

 A dosage form as defined in claim 4, further comprising a flavoring agent.

 A dosage form as defined in claim 6, wherein said flavoring agent is a flavor system consisting of cherry, vanilla, and benene.

 A dosage form as defined in claim 4, in the form of a suspension made from said powder.

 An oral desage form of szithrumycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a maranul that has caten, which

comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dusage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azkitromycin is tested as set furth in USP test <7(1)> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml scallers prosphate buffer, pli 5.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains

23

icas them a teste-marking amount of an alkaline curtis metal oxide or hydroxide. A douge form as defined in claim 9, wherein said mammal is a human.

11. A dosage form as defined in claim 9, further commis-

ing an anhydrous buffer.

12. A douage form as defined in claim 9, wherein said 15 dispersing agent is colloided silicon dioxide.

13. A dosage form as defined in claim 9, in the form of a suspension made from said unit dose packet.

14. An oral dosage form of azilhronycin which is in the form of a tablet made by wet granulation, which is admin- 20 istrable to a mammal that has caten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form exhibiting a value of (AUC, MAUC,) of at least (1.80) with a lower 90% confidence limit of at least 0.75, provided that said dosage form 25 contains less than a taste-marking amount of an alkaline carth metal oxide or hydroxide.

15. A dosage form as defined in claim 14, wherein said mammal is a ligman.

16. A dosage form as defined in claim 14, further com- 30 prising a flavoring agent.

17. An oral dosage form of azithromycin which is in the form of a powder for oral suspension containing an anhydrous buffer, which is administrable to a mammal that has caten, which comprises azithromycin, one or more thicken- 35 ing agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form exhibiting a value of (AUC, MAUC,) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form commins less than a taste-masking amount of an alkaline 40 carth metal exide or hydroxide.

18. A dosage form as defined in claim 17, wherein said managal is a human.

19. A dosage form as defined in claim 17, further compristing a flavoring agent.

20. A dorage form as defined in claim 19, wherein said flavoring agent is a flavoring system consisting of cherry, vanilla, and banana.

21. A dorsee form as defined in claim 17, in the form of a suspension made from said powder.

21. An oral desage form of szithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has caten, which comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dosage form so exhibiting a value of (AUC,)/(AUC,) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that sald dosage form contains less than a taste-masking amount of an alkaline earth metal exide or hydroxide.

23. A dosage form as defined in claim 22, wherein said 60 mammal is a human.

24. A desage form as defined in claim 22, further comprising an unhydrous buffer.

25. A dosage form as defined to claim 22, wherein said dispersing agent is colloidal silicon dioxide.

26. A douage form as defined in claim 22, in the form of a suspension made from said unit dose packet,

24

27. A dosage form as defined in claim 1, comprising: 58.2% azithromycin dibydrate;

6.0% prevelatinized sturch:

30.9% anhydrous dibasic calcium phosphate;

2.0% sodium croscarmellose; and

2.9% Jubricant.

28. A dosage form as defined in claim 1, comprising: 58.2% azithromycin dihydrate;

11.1% pregelatioized starch;

25:7% unhydrous dibasic calcium phospitute;

2.0% sodium croscermellose; and

2.9% lubricant.

29. A dosage form as defined in claim 1, comprising:

58.2% azithromycin dihydrate;

3.1% pregelatinized starch:

31.3% unhydrous dibasic calcium phosphase;

4.4% sodium croscarmellose; and

2.9% lubricant

30. A dosage form as defined in claim 1, comprising:

58.2% azithromycin dibydrate;

11.1% preactatinized starch;

23.3% anhydrous dibasic calcium phosphate;

4.4% sudium croscamiellose; and

2.9% lubricunt

31. A dosage form as defined in claim 1, comprising:

58.2% azithromycin dihydrate:

3:1% maize starch:

33.8% dibasic calcium phosphate, lactose, or microcrystalline cellulose:

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

32. A dosage form as defined in claim 1, comprising:

58,2% azithromycin dihydrate;

6.0% plaine starch:

30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose:

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricare.

A dosage form as defined in claim 1, comprising:

58.2% azithromycin dihydrate;

11.1% maize starch:

25.7% dibasic calcium phosphiae, lactore, or microcrystalline cellulose;

2.0% sodium starch glyculate or crosslinked polyvinylpyrrolidone; and

2.9% Inbricant.

34. A dosage form as defined in claim 1, committing: 58.2% azithromycin dihydrate;

3.1% maize starch;

31.3% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

4.4% sodium march glycolate or crosslinked polyviny)pytrolidone; and

2.9% lubricant.

35. A dosage torm as defined in claim 1, comprising:

58.2% azithromycin dihydrate;

6.0% maize stands:

25 26 32.2% dihasic calcium phosphate, factose, or microcrys-42. A dosage form as defined in claim 4, comprising: talline cellulore; 5.0% axithromycin dihydrate; 0.7% sodium starch glycolate or crosslinked polyvi-46 3% sorbital: nylpyrrolidone; and 46.3% sucrose; 2.9% lubricant. 0.4% anhydrous tribasic sodium phosphate: 36. A dosage form as defined in claim 1, comprising: 0.2% hydroxypropylmethylcellulose; 58.2% aziıbromycin dihydrau; 0.2% xanthan gum; and 6.0% maize starch; trace coloring 28.4% dibasic calcium phrisphate, lactose, or microcrys-1.8% flavoring. talline cellulose; • 43. A dusage form as defined in claim 4, comprising: 4.4% sodium starch glycolate or crosslinked pulyvi-5.0% azithromycin dihydraic; aylpyrrolidone; and 45.7% ынтове; 2.9% lubricant. 45.7% sochital: 37. A dosage form as defined in claim 4, comprising: 15 0.9% anhydrous sodium carbonate; 5.0% azithromycio dibydraic; 0.2% anhydrous tribasic sodium phosphate; 92.5% sucrose: 0.1% hydroxypropylmethylcellulose; 0.4% enhydrous tribasic sodium phosphote; 0.1% xanthan gum; 0.2% hydroxypropylcoliulose: 0.1% sodium carboxymethyleellulose: 0.2% zenthen gum; 0.1% colloidal silicon dioxide; trace coloring; and 0.3% glycine; 1.8% flavoring. trace coloring; and ... 38. A dosage form as defined in claim 4, comprising: 1.8% flavoring. 4.8% azithromycin dibydrate; 44. A dosage form as defined in claim 9, comprising: 58.0% sucrose: 9.5% azithromycin dihydrate; 29.0% sorbital; 88.2% sucrose; 1.9% anhydrous sodium carbonate; 0.8% anhydrous tribasic sodium phosphate; 0.4% sodium benzoate; 0.5% colloidal silicon dioxide; and 1.5% tragacanth gum powder; 0.9% flavoring. 1.5% titanium dioxide; 45. A dosage form as defined in claim 9, comprising: 1.15% colloids! silicos dioxide; 9.5% azithromycin dihydrate; 0.6% glycine; and 88.29; surbital: 2.3% flavoring. 0.8% anhydrous tribasic sodium phosphate; 39. A douge form at defined in claim 4, comprising: 0.5% colloidal silicon dioxide; and 5.0% azithromycin dihydrate; · 0.9% flavoring. 91.8% meraje; 46. A dosage form as defined in claim 9, comprising: 0.4% anhydrous tribasic sodium phosphate; 9.6% azithromycin dihydrate; 0.2% hydroxypropylcellulose: 88.9% sucrose; 0.2% xanthan gum; 0.4% anhydrous tribasic sudium phosphate; 0.1% colloidal silicon dioxide; 0.2% colloidal silicon dioxide; and 0.6% glycine; 0.9% flavoring. trace coloring; and 47. A dosage form as defined in claim 9, comprising: 9.3% azithromycia dihydrate; 49. A dosage form as defined in claim 4, comprising: 86.1% sucrose; 5.0% szithromycin dibydrate; 1.8% anhydrous tribasic sodium phosphate; 92.5% suzque; 2.0% calloidal silicon dioxide; and 0.4% anhydrous tribasic sodium phosphate; 0.9% flavoring. 0.3% sodium carbuxymethylcellulose; 48. A dosage form as defined in claim 9, comprising: trace coloring; and 16.7% azithromycin dihydrate; 1.8% flavoring. 79.5% sucrose; 41. A dosage form as defined in claim 4, comprising: 1.4% anhydrous tribusic sodium phosphate; 5.0% azithromycin dihydrate; 0.9% colloidal silicon diuxide; and 90.4% sorbitol; 1.6% flavoring. 1.8% anhydrous sodium carbonate; 49. A dosage form as defined in claim 9, comprising: 0.3% sodium carboxymethylceliulose; 9.5% azithromycin dihydrate; 0.1% colloidal silicon dioxide: 44.1% aucrosc: 0.6% glycine; 44.1% sorbitol; trace coloring; and 0.8% anhydrous tribasic sodium phosphate; 1.8% Savoring. 0.5% colloidal allicun dioxide; and

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5,605,889

Document 13-2

28 27 58.2% azithromycin dibydrate; 0.9% flavoring 50. A dosage form as defined in claim 9, comprising: 3.1% maize starch; 9.5% azithromycin dihydrate; 31.3% dibasic calcium phosphate, lactore, or microcrystalline cellulose; 44.1% sucrose; 4.4% sodium starch glycolate or crosslinked polyvi-44.1% sorbitol; 0.4% anhydrous tribasic sodium phosphate; nylpymolidone; and 2.9% Jubricani. 0.2% achydrons sodium carbonate; 59. A dusage form as defined in claim 14, comprising: 0.2% glycine; 58.2% azithromycin dihydrate; 0.5% colleidal silicon dioxide; and 6.0% maize starch: 0.9% flavoring. 51. A dosage form as defined in claim 14, comprising: 32.2% dibasic calclum phosphate, lactose, or microcrystalline cellulose; 58.2% azithromycin dihydrate; 6.0% pregclatinized starch; 0.7% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and 30.9% anhydrous dibasic catcium phosphate; 2.9% lubricant. 2.0% andiom croscarmellose; and 60. A dosage form as defined in claim 14, comprising: 2.9% Jubricant. 52. A dusage form as defined in claim 14, comprising: 58,2% azithromycin dibydrate; 6.0% maize starch: 58.2% szithromycin dihydrate; 28.4% dibasic calcium phosphate, lactose, or microcrys-11,1% pregelatinized starch; talline cellulose; 25.7% anhydrous dibasic culcium phosphaie; 4.4% sodium starch glycolate or crosslinked polyvi-20% sodium croscarmellose; and nylpymolidouc; and 25 2.9% lubricant 2.9% lubricant. 53. A desage form as defined in claim 14, comprising: 61. A dosage form as defined in claim 17, comprising: 58.2% azithromycin dihydrate; 5.0% uzidiromycin dihydrate; 3.1% progalutinized starch; 92.5% sucrose: 31.3% anhydrous dibasic calcium phosphate; 0.4% anhydrous tribasic sodium phosphate; 4.4% sodium croscarmellose; and 0.2% hydroxypropylcellulose; 29% lubricant 0.2% auniban gum; 54. A dosage form as defined in claim 14, comprising: trace culoring; and 58.2% azithromycin dihydrate; 1.8% flavoring. 11,1% progelatinized starch: 62. A dosage form as defined in claim 17, comprising: 23.3% anhydrous dibasic calcium phosphate: 4.8% azithromycin dibydrate; 4.4% sodium croscarmellose; and 58.0% sucrose; 2.9% Jubricant 29.0% sorbitol; 55. A dosage form as defined in claim 14, comprising: 1.9% anhydrous sodium carbonate; 58.2% szithromycia dihydrate; 0.4% sodium benzoate; 3.1% maize starch; 1.5% tragacanth gum powder; 33.8% dibasic calcium phosphate, lactose, or microcrys-1.5% titunium dloxide; taliine cellulose; 1.15% cultoidal silicon dioxide; 2.0% sodium starch glycolate or crosslinked polyvi-0.6% glycine; and nylpymolidone; and 2.9% lubricant 2.3% flavoring. 63. A dosage form as defined in claim 17, comprising: 56. A dosage form as defined in claim 14, comprising: 58.2% azithromycin dlhydrate; 5.0% azithromycin dihydrate; 6.0% maize starch: 91.8% microsc: 30.9% dibesic calcium phoephate, lactose, or microcrys-0.4% anhydrous tribatic sodium phosphate; cultine celtulose; 0.2% hydroxypropylectiulose; 2.0% sodium starch glycolate or crosslinked polyvi- >> ().2% ranthan gum; nylpymulidone; and 0.1% colloidal silicon dioxide; 2.9% lubricant. 0.6% glycinc; 57. A dosage form as defined in claim 14, comprising: trace coloring; and 58.2% azithromycin dihydrate; 1.8% flavoring. 11.1% maize starch; 64. A dosage form as defined in claim 17, comprising: 25.7% dibasic calcium phosphate, lactore, or microcrys-5.0% azithromycia dihydrate; jalline cellulote; 92.5% sucroce; 2.0% sodium starch glycolate or crosslinked polyvi-0.4% aphydrous tribasic sodium phosphate; nylpyrrolidene; and 0.3% sodium carboxymethylcollulose; 2.9% Jubricant. trace coloring; and 58. A desage form as defined in claim 14, comprising:

29

79.5% sucrose; ·

1.8% flavoring 65. A dosage form as defined in claim 17, comprising: 5.0% withromyein dihydrate; 90.4% aorbito); 1.8% anhydrous sodium carbonate; 0.3% sodium carboxymethylcelluluse; 0.1% colloidal silicon dioxide; 0.6% glycine; trace coloring; and 1.8% flavoring.

66. A duage form as defined in claim 17, comprising: 5.0% azithromycin dibydrate;

46.3% sorbitol:

46.3% sucrise;

0.4% anhydrous tribasic sodium phosphate;

0.2% hydroxypropylmethylcellulose;

0.2% xanthun gum; and

trace coloring

1.8% flavoring

67. A dosage form as defined in claim 17, comprising:

5.0% azlthromycin dihydrute;

45.7% aucrose: -

45.7% sorbital:

0.9% anhydrous sódium carbonate;

0.2% anhydrous tribasic sodium phosphate;

0.1% hydroxypropylmethyk:ellulose;

0.1% xanıbun gum;

0.1% audium carboxymethyleellulose;

0.1% colloidal ailicon dinnide;"

0.3% glycine;

trace coloring; and

1.8% flavoring.

68. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dihydrate;

88.2% sucrose;

0.8% anhydrous tribusic sudium phosphale;

0.5% colleidal silicem dinxide; and

0.9% flavoring.

69. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dihydrate;

88.2% sorbitol;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloided silicon dioxide; and

0.9% flavoring.

70. A dosage form as defined in claim 22, comprising: 9.6% azithromycin dihydrate;

88.9% sucrose;

0.4% anhydrous tribusic sodium phosphate;

0.2% colloidal silicon dioxide; and

0.9% flavoring.

71. A dosage form as defined in claim 22, comprising:

9.3% azithromycin dihydrate;

86.1% sucrose;

1.8% anhydrous tribusic andium phosphate;

2.0% colloidal silicon dioxide; and

0.9% flavoring.

72. A dosage form as defined in claim 22, comprising:

16.7% uzithromycia dihydrate;

1.4% anhydrous tribasic sodium phusphate;

0.9% colloidal silicon dioxide; and

1.6% flavoring.

73. A dosage form as defined in claim 22, comprising:

30

9.5% azithromycin dihydrate;

44.1% tuerose;

44.1% sorbitol;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

74. A dosage form as defined in claim 22, comprising:

9.5% azithromycln dihydrate;

44.1% sucrose;

44.1% sorbitol:

0.4% anhydrous tribasic sodium phosphate:

0.2% anhydrous sodium carbonate;

0.2% glycine;

0.5% colloids! silicon dioxide; and

0.9% flavoring.

75. A therapeutic package, comprising

a container,

an oral dosage form of azithromycin which exhibits either or

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both of: (a) at least about 90% dissolution of azithromychi within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as act forth in USP test <711> in a USP-2

dissolution apparatus under conditions at Icast as stringent as the following: 900 ml sodium phosphai buller, pli 6.0, 37° C., with paddles turning at 100 rom: and/or

(b) a value of (AUC_{fee})/(AUC_{fee}) of at least 0.80 with a lower 90% confidence limit of at least 0.75.

and, associated with said package, written matter nonlimited as to whether the desage form can be taken with or without food.

76. A therapeutic package as defined in claim 75, wherein said dorage form is in the form of a tablet.

77. A therapeutic package as defined in claim 75, wherein said desage form is in the form of a powder for oral suspension.

78. A therapeutic package as defined in claim 77, wherein said dosage form is in the form of a suspension made from sald powder.

A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a unit dose packet.
 A therapeutic package as defined in claim 79, wherein

said dosage form is in the form of a suspension made from said unit dose packet.

81. A method for treating a microbial infection in a mammal which comprises administering, to a manual that has eaten in need of such treatment, an antimiembially effective amount of azithromycle in an oral desage form which exhibits either or both of:

(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithrumycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37" C., with paddles turning at 100 span; and/or

(b) a value of (AUC_{fee})/(AUC_{fee}) of at least 0.80 with a lower 90% contidence limit of at least 0.75.

(12) United States Patent Allen et al.

(10) Patent No.: (45) Date of Patent:

US 6,268,489 B1 Jul. 31, 2001

(54)	AZITHRO	OMYCIN DIHYDRATE	(56) References Cited
(75)	Inventors:	Douglas J. M. Allen, New London; Kevin M. Nepvenx, Old Saybrook, loah of CT (US)	U.S. PATENT DOCUMENTS 4/1927
(73)	Assignce:	Pfixer Inc., New York, NY (US)	4,512,982 * 4/1985 Hausir et al
(*)	Nozice:	Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	4,963,531 7/1985 Bright 514/29 4,963,531 10/1990 Remington 514/29 OTHER PUBLICATIONS
(21)	Appl. No.:	07/994,040	Peljaza et al., Farmaco Ed.Sc., 31, 254-262 (1976). Allen et al., J. Pharm. Sci., 67, 1087-1093 (1978).
(22)	Filed:	Dec. 21, 1992	* cited by examiner
	Rel	uted U.S. Application Data	Primary Examiner -Elli Pesclev
(63)	Continuation	a of application No. 07/449,961, filed on Dec.	(74) Attorney, Agent, or Firm—Peter C. Richardson; Gregg C. Beusun; Mervin E. Brokke
(30)	•	ga Application Priority Data	(57) ABSTRACT
Ju (51) (52)	Int. Cl.7 U.S. Cl	(WO) RT/US87/01612 C07H 17/08 536/7.4; 536/18.5	Non-hygroscopic, azithromycin (9-deoxo-9a-aza-9a- methyl-9a-homoerylluomycin) dihydrate and a process therefor.
(58)	Field of S	earch 536,7.4, 18.5	3 China, No Drawings

US 6,268,489 B1

AZITUROMYCIN DITIYDRAFE

This is a continuation of application Ser. No. 07/449,961, filed on Dec. 11, 1989 now abandoned as a request for U.S. 3 examination of International Application No. PCT/US87/ (11612, filed Jul. 9, 1987.

BACKGROUND OF THE INVENTION

The present invention is directed to a valuable new form of azithromycia (9-dcoxo-9a-aza-9a-methyl-9ahomostythromycin A), viz., a non-hygroscopic dihydrate 18 form thereof.

Azithromycin is the U.S.A.N. (generic name) for 30 9-deoxo-9a-aza-9a-methyl-9a-homocrythromycin A, a broad spectrum antibacterial compound derived from crythcompoin A. Azithromycia was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kebrehelet al., U.S. Pat. 25 No. 4,517,359. The name "N-methyl-11-aza-10-deoxo-10dihydrocrythromycin A" was amployed in these patents. The present more systematic name is based upon the ring expansion and replacement nomenclature of the "IUPAC Nomenclature of Organic Chemistry, 1979 Edition," Pergamon 30 Press, 1979, pp. 68-70, 459, 500-503.

As previously crystallized from ethanol and water (e.g., 35 ranges near that of pure n-hexane. Example 3 of U.S. Pat. No. 4,474,768), azithromycin was chiained as a hygroscopic monohydrate (for details, see Preparation 1 below). Hecause of its hygroscopic nature, it is most difficult to prepare and maintain this prior monohydrate product in a form having a constant, reproducible an water-content. It is particularly difficult to handle during formulation, since at higher relative humidity levels which are generally required to avoid electrostatic problems (e.g., flow rates, dusting with potential for explosion), the monohydrate readily picks up varying amounts of water, the amount depending upon exposure time and the precise value of the relative humidity (see Preparation 1 below). Such problems have been overcame by the present invention of a stable dihydrate which is essentially non-hygroscopic under (8) conditions of relative humidity conducive to formulation of azithmnycin-

SUMMARY OF THE INVENTION

The present invention is directed to a valuable new form of azithromycio, viz., a crystalline, non-hygroscopic dihydrate, prepared by crystallization from tetrahydrofuran and an aliphatic (C3-C3)hydrocarbon in the presence of at least two molar equivalents of water.

2 Azithromycia is of the formula

It is derived from crythromycin A without involvement of asymmetric centers, and so has stereochemistry at each of these centers (*) which is identical with that of crythromycin A. Named systematically as an ecythromycin A derivative, the compound is called 9-deoxo-9a-aza-9a-methyl-9ahomocrythromycin A. Azithromycin, including the present dihydrate, possess broad-spectrum antibacterial activity useful in the treatment of susceptible bacterial infections in mammals, including man.

The expression "aliphatic (Cs-C7)hydrocarbon" refers to lower boiling bydrocarbon solvents, frequently mixtures of particular boiling point ranges such as those generally referred to as "pentane", "hoxane", "hexanes", etc., but which may also be substantially pure, e.g., n-hexane, cyclohexane or methylcyclohexane. A preferred hydrocarbon solvent is so-called "hexage", having a boiling point which

DETAILED DESCRIPTION OF THE ΙΝΥΈΝΠΟΝ

The present invention is readily carried out. Azithromycin, prepared accarding to Bright or Kobrehel et al. (cited above) in amorphous form, or as the monohydrate (which may contain, because of its hygmscopicity, more than one molar equivalent of water) is dissolved in tetrahydrofuren. Since the temperatures required for the initial stages of the present process are not critical, ambient temperatures are generally employed, avoiding the cost of heating and cooling, Furthermore, to maximize yield and minimize solvent, labor and equipment costs, the volume of tetrahydrofuran is kept to a near minimum, e.g., 2 liters of solvent per kilogram of substrate. Any insoluble impurities which may be present at this stage are readily removed by conventional methods of filtration. If necessary, the mixture can be decolorized with activated carbon. If desired, the highly concentrated mixture can be diluted with a portion of (C.-C.)hydrocarbon prior to filtration, in order to facilitate handling. If the water content of the ingoing bulk is much greater than one molar equivalent, e.g., approaching 2-molar equivalents, it is preferable to dry the mixture for a short riod of time over a drying agent such as MgSO4, partieslarly if hydrocarbon solvent is to be added prior to filtration. To obtain the crystalline dihydrate, water is added to the resulting clear solution, in an amount sufficient to bring the total water content to a level corresponding to at least two molar equivalents, generally not exceeding a level of about 3-4 molar equivalents. The level of water present in the

US 6,268,489 B1

3

system is readily monitored by standard Karl Pischer titration. The addition of water is followed by the addition of the hydrocarbon solvent (or of more hydrocarbon solvent, if the mixture was previously diluted before filtration), leading to crystallization of the desired dihydrate product. This stage of 3 the process can be carried out at ambient temperature (e.g. 17-30° C.), but to facilitate the mitial crystallization, is preferably carried at slightly elevated temperature (e.g. 30-40° C.). The total volume of hydrocarbon solvent compleyed is generally at least about four times in volume 10 that of the tetraligidations. Higher volumes of hydrocarbon are satisfactory, but are generally avoided in the interest of minimizing cost. Once crystallization is complete, the product is recovered by filtration, usually after a period of granulation (e.g., 3-24 hours) at ambient temperature. The 15 product is usually vacuum dried of organic solvents (a) 20-40° C., conveniently at ambient temperature). To avoid loss of water of hydration, the volutiles and water-content are generally manitoned during drying, such that the level of tetrahydrofuran and hydrocarbon will generally fall below 20 0,25% and the water content will be within 0.3% of theory (4.6 £).

Azithromycin dihydrate is formulated and administered in the treatment of susceptible bacterial infections in man according to methods and in amounts previously detailed by 25 Bright, U.S. Pat. No. 4,474,768, cited above and hereby incorporated by reference

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

EXAMPLE 1

Non-Hygroscopic Azithromycin Dihydrate

Method A

The hygroscopic monohydrate of Preparation 1 (100 g; water-content.3.194), tetrahydrofuran (220 ml) and diatomaceous earth (5 g) wore combined in a 500 ml Erlemmyer flask, stirred for 30 minutes and filtered with 20 ml of tetrahydrofuran wash. The combined filtrate and wash was transferred to a 3 liter round bottom flask. The solution was stirred vigorously and H₂O (2.0 ml) was added. After 5 minutes, became (1800 ml) was added over 5 minutes, with continued vigorous stirring. Following an 18 hour granulation period, title product was reconverted by filtration with 1x10 ml became wash, and dried in vacuo to 4.6x0.2% H₂O by Karl Fischer, 89.5 g.

Method II

The hygrescopic monohydrate of Preparation 1 (197.6 g) so and (etrahydrofuran (430 nt)) were charged to a reactor and the mixture stirred to achieve a milky white solution. Activated carbon (10 g) and diatomaceous earth (10 g) were added and the mixture stirred for 15 minutes, then diluted with 800 ml of hexane and lillered with suction over a pad of diatomaceous earth with 250 ml of hexane for wash. The combined filtrate and wash was diluted to 2500 ml with hexane and warmed to 34° C. With stirring, 24.7 ml of H₂O was added. The mixture was allowed to cool to coom temperature, granulates for live hours and title product on recovered and dried as in Method A, 177.8 g.

The dihydrate melts sharply at 126° C. (hot stage, 10°/minute); differential scanning calorimetry (heating rate, 20° C./minute) shows an endotherm at 127° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows a 1.8% as weight less at 100° C. and a 4.3% weight loss at 150° C.; ir (Klir) 3953, 3553, 3488, 2968, 2930, 2888, 2872, 2827,

2780, 2089, 1722, 1664, 1468, 1426, 1380, 1359, 1344, 1326, 1318, 1282, 1270, 1252, 1187, 1167, 1157, 1123, 1107, 1082, 1050, 1004, 993, 977, 955, 930, 902, 986, 879, 864, 833, 803, 794, 775, 736, 729, 694, 671, 661, 637, 598, 571, 526, 495, 459, 399, 374, 321 and 207 cm⁻¹; [atphu]²⁶p-41.4° (c=1, CHCl₃).

Anal. Cated. for C₃₈H₂N₃O₁₂-2H₂O: C, S8.14; H, 9.77; N, 3.57; OCH₃, 3.95; H₂O, 4.59. Found: C, S8.62; H, 9.66; N, 3.56; OCH₃, 4.11; H₂O, 4.49. Neutralization Equivalent (0.5N IICt in 1:1 CH₂CN:H₂O): Cated.: 374.5. Found: 103.4

Samples of a dihydrate, alightly over dried to contain 4.1% water (less than theoretical) rapidly picked-up water at 33%, 75% or 100% relative humidities to achieve the theoretical water content (4.6%) for the dihydrate. At 33% and 75% relative humidities, water content remained essentially constant for at least 4 days. At 100% relative humidity, the water content further rose to about 5.2, where it remained essentially constant of the next three days.

A sample of the same dibyrate, maintained at 18% relative bunidity gradually lost water. At four days, the water content was 2.5% and at 12 days, 1.1%.

PREPARATION I

Hygrascapic Azithromycin Monobydrate

Substantially following the methylation procedure of Kobrehel et al., U.S. Pat. No. 4,517,359; and the crystallization procedure of Bright, U.S. Pat. No. 4,474,768; 9-denxo-9a-aza-9a-homocrythromycia A (previously called 11-aza-10-denxo-10-dihydrocrythromycia A; 100 g, 0.218 niol) was dissolved with stirring in 400 ml CIICls. Formic 35 acid (98%; 10.4 ml, 0.436 mol) and formuldehyde (37%; 16.4 ml, 0.349 mol) were added over 4-5 mimites, and the mixture heated at reflux for 20 hours. The mixture was cooled to ambient temperature, diluted with 400 ml $m H_2O$ and adjusted to pH 10.5 with 50% NaOH. The aqueous layer was separated and extracted 2x100 ml with fresh CHCl3. The organic layers were combined, stripped in vacuo to 350 ml, twice diluted with 450 ml of ethanol and restripped to 350 mi, and finally diluted with 1000 ml H2O over a 1 hour period, passing for 15 minutes as a slarry began to develop after the addition of about 250 ml of H₂O. Title product was recovered by filtration and dried in air at 50° C. for 24 hours, 85 g; mp 130° C.; differential thermal enalysis (heating rate 20° ("Iminute) shows an endotherm at 142° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows 2.6% weight loss at 100° C, and a 4.5% weight loss at 150° C.; water content 3.92%; ethanol content 1.09%.

Anal. Calcd. for $C_{3a}H_{72}N_2O_{12}$ (connected for ethanol and water content): C, 58.46; H, 9.78; N, 3.74; Alkoxy, 4.67. Found: C, 58.40; H, 9.29; N, 3.50; Alkoxy, 4.52.

A sample of the monohydrate (having a water content of 3.2%) was maintained at 18% relative humidity for 14 days. The sample lost water over the first 24 hours to yield monohydrate having the theoretical water content (2.35%). The water content then remained substantially constant over 14 days, a value of 2.26% being recorded at 14 days.

At 33% relative humidity the water content of a sample of the same monohydrate rapidly rose to 5.6% where it remained substantially steady for at least three days. Sknilarly at 75% and 100% relative humidity, the water content rose rapidly, but was now maintained at even higher levels, 6.6% and 7.2%, respectively, for at least 3 days.

US 6,268,489 BI

What is claimed is: 1.

1. Crystalline azithromycin dihydrate.

2. A method of preparing crystalline azithromycin dihydrate which comprises crystallization of amorphous azithromycin or azithromycin monohydrate from a mixture of

tetrahydrofuran and a (C₂-C₂) aliphatic hydrocarbon in the presence of at least 2 molar equivalents of water.

3. A method of claim 2 wherein the hydrocarbon is

tiexane.



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August 5, 2003

By Hand

Jeffrey B. Kindler, Esq.
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Re: Azithromycin - U.S. Patent Nos. 5,605,889 and 6,268,489

Dear Mr. Kindler:

We represent Teva Pharmaceuticals USA, Inc ("Teva"). We write concerning U.S. Patent Nos. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," and 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," both of which are assigned on their face to Pfizer, Inc.

On December 12, 2002, Teva filed with the FDA Abbreviated New Drug Application ("ANDA") No. 65-153 for 250 mg azithromycin tablets. On November 27, 2002, Teva filed ANDA No. 65-150 for 600 mg azithromycin tablets. Teva expects the FDA to approve these ANDAs in due course.

By filing these ANDAs, Teva has made substantial preparations to make, use, offer to sell, sell, and/or import a generic version of ZITHROMAX. By filing these ANDAs with the intent to obtain approval to market prior to the expiration of the '489 and '889 patents, Teva has committed a technical act of infringement of these patents. In light of these activities, Teva requests that Pfizer grant a covenant to Teva that Pfizer will not enforce the '889 and '489 patents against Teva for having made, making, using, offering for sale, selling, or importing the azithromycin tablets described in Teva's ANDA Nos. 65-153 and 65-150.

Pfizer has sued Novopharm, Teva's Canadian affiliate on the Canadian equivalent of the '489 patent. Based on the information available to Pfizer as a result of that suit, Teva believes that Pfizer has sufficient information to determine whether it believes Teva's manufacture, use, importation, or sale of the azithromycin products covered by the ANDAs infringe the '889 and/or '489 patents. However, should you require further information, Teva will provide to Pfizer, upon execution of an appropriate confidentiality agreement, information regarding the formulation of the products described in Teva's ANDAs, the bioequivalency data included in the ANDAs, and samples of (i) the products described in the ANDAs, (ii) the raw materials used to make those products, and (iii) azithromycin ethanolate monohydrate, the active ingredient in the products described in the ANDAs.

aey B. Kindler قد ast 2, 2003 age 2 of 2



We are prepared to send Pfizer these materials immediately upon execution of an appropriate confidentiality agreement. For your convenience, we attach a form confidentiality agreement. However, we will disclose these materials under any reasonable terms. If our letter is unsatisfactory, please propose an acceptable alternative.

In view of the urgent need to resolve issues of potential patent infringement prior to Teva's marketing of its azithromycin products, we ask that you respond to this letter within forty five (45) days of receipt. If we do not receive a reply within this time frame, we will take appropriate legal action.

Very truly yours, `

Steven J. Lee

.ce: Richard Egosi, Esq.

Enclosure :

CONFIDENTIALITY AGREEMENT

This Confidentiality Agreement is executed by and between TEVA Pharmaceuticals USA ("Teva"), PFIZER, INC. ("Pfizer"), and Counsel therefore.

RECITALS

WHEREAS, pursuant to § 505(j), Title 21 of the Federal Food, Drug and Cosmetic Act ("the Act"), Teva has filed abbreviated new drug applications, ANDA Nos. 65-153 and 65-150, to obtain approval to engage in the commercial manufacture, use, sale, and importation of azithromycin before the expiration of U.S. Patent Nos. 5,605,889 ("the '889 patent") and 6,268,489 ("the '489 patent").

WHEREAS, Pfizer owns the '889 and '489 patents.

WHEREAS, Pfizer manufactures and markets a pharmaceutical product called Zithromax® (azithromycin) and owns and/or controls certain patent rights, trademarks and know-how relating thereto, including the '889 and '489 patents.

WHERAS, by letter dated August 5, 2003, Teva offered Pfizer certain confidential information of Teva with respect to ANDA Nos. 65-153 and 65-150 and the product Teva proposes to sell thereunder ("Teva Confidential Information") to allow Pfizer to evaluate whether it believes the commercial manufacture, use, sale, or offer for sale in the United States, or the importation into the United States of the azithromycin products described in its ANDAs will infringe, contribute to or induce the infringement of the '889 and '489 patents.

WHEREAS, Teva will provide Counsel for Pfizer with sufficient of Teva's Confidential Information to permit them to conduct an evaluation under appropriate confidentiality provisions as set forth herein.

NOW THEREFORE, in consideration of the mutual covenants herein contained, the parties mutually agree as follows:

- 1. Teva shall promptly provide to Counsel for Pfizer a copy of documents sufficient to describe in detail formulation of Teva's proposed azithromycin product, including but not limited to the components of the formulation, the percentage of each component used in the formulation and the process by which Teva prepares the proposed azithromycin product; one (1) 50 tablet sample from each lot of Teva's azithromycin tablets, including 250 mg and 600 mg, including one (1) 50 tablet sample from each lot which was submitted to the FDA, or as to which information was submitted to the FDA in connection with ANDAs 65-153 and 65-150, as well as samples of the raw materials used to make those tablets; and the bioequivalency data included in ANDA Nos. 65-153 and 65-150.
- 2. Counsel for Pfizer shall use the Teva Confidential Information referenced in Paragraph 1 herein for the sole purpose of evaluating whether it believes the commercial

manufacture, sale, or offer for sale within the United States, or the importation into the United States, of the azithromycin products described in ANDA Nos. 65-153 and 65-150 will infringe. contribute to, or induce the infringement of the '889 and '489 patents. At the conclusion of such evaluation, but in no event later than September 19, 2003, Counsel for Pfizer shall destroy or return all Teya Confidential Information.

- Counsel for Pfizer may not disclose Teva's confidential information to Pfizer or 3. any other party, except that Counsel for Pfizer may disclose the physical samples to Pfizer employees for the purpose of conducting in vitro tests, and may disclose any of the confidential information, including the physical samples, to independent experts not associated with Pfizzar. Such experts must first be identified to Teva, and Teva must have 5 business days within which to object to such experts. Such experts must be made aware of this agreement and must agree to abide by its terms. Counsel for Pfizer agrees to not disclose, communicate or cause to be communicated to any third party, in any manner whatsoever, any and all of the Teva Confidential Information without receiving the prior written consent of Teva to use such Confidential Information. Counsel for Pfizer will not disclose any of Teva's Confidential Information for any reason whatsoever except as set forth above. Samples of Teva's azithromycin and azithromycin products are not yet approved for marketing in the United States, and may not be administered to human patients or subjects.
- Counsel for Pfizer shall have no obligation to Teva under this Agreement to maintain the confidentiality of information that:
- can be demonstrated to have been in the public domain prior to execution of this Agreement;
- can be demonstrated to have been in possession, either through independent development or from another source not under obligation of secrecy to Teva prior to disclosure of Teva's Confidential information under this Agreement; or
- becomes part of the public domain by publication or otherwise, not due to any unauthorized acts by Counsel for Pfizer.
- Counsel for Pfizer, and any independent experts retained by them, agree to maintain the confidentiality of all of Teva's Confidential Information received under the terms of this Agreement unless instructed otherwise by Teva in writing.
- This Agreement constitutes the entire agreement between the parties and supersedes all previous agreements and understandings relating to the subject matter hereof. This Agreement can only be modified by a writing signed by both parties hereto.
- This Agreement may be executed by facsimile signatures and/or in counterparts and will become effective upon the date execution has been made by the last party whose execution is required, each such counterpart of which shall be an original, but all of which constitute one agreement.

		ı		••	
ACC	EPTED A	ND A	REE	D TO:	
PFIZ	ER, INC.	•	* .		
By:					
Title:		_			
Date:			,		
TEVA	A PHARM	IACEU	TICA	LS USA	ת,
Ву:					
Title:					

EXHIBIT C

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., Plaintiff,))))
v.	Civil Action No. 03-CV-7423 (LAP)
PFIZER INC.,))
Defendant.)

ANSWER AND COUNTERCLAIMS OF PFIZER INC.

Defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, for its answer to the complaint for declaratory judgment ("Complaint") of plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), responds as follows:

- Pfizer admits the allegations contained in paragraph 1 of the Complaint. 1.
- Pfizer admits the allegations contained in paragraph 2 of the Complaint. 2.
- Pfizer admits the allegations contained in paragraph 3 of the Complaint. 3.
- Pfizer admits the allegations contained in paragraph 4 of the Complaint. 4.
- Pfizer admits the allegations contained in paragraph 5 of the Complaint. 5.
- Pfizer admits that this Court has original jurisdiction over matters arising under 35 6. U.S.C. § 1 et seq., but denies that this Court has jurisdiction over the subject matter of this declaratory judgment action.
- Pfizer admits that Teva filed this declaratory judgment action for non-7. infringement and invalidity but denies the remaining allegations contained in paragraph 7 of the Complaint.

- Pfizer admits the allegations contained in paragraph 9 of the Complaint. 9.
- Pfizer admits the allegations contained in paragraph 10 of the Complaint. 10.
- Pfizer is without knowledge or information sufficient to form a belief as to the 11. truth of the allegations contained in paragraph 11 of the Complaint.
- Pfizer admits that azithromycin is a component of Pfizer's Zithromax® product, 12. admits that United States Patents Nos. 5,605,889 (the "'889 patent") and 6,268,489 (the "'489 patent") relate to azithromycin, denies that the phrase "contain claims directed to azithromycin" is an accurate description of the claims of the patents, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in paragraph 12 of the Complaint.
- Pfizer admits that it initiated a proceeding in Canada under Canadian law against 13. the Canadian Minister of Health and Novopharm regarding Novopharm's Notice of Allegation concerning the Canadian counterpart to Pfizer's '489 patent. Pfizer affirmatively states that such proceeding is not an action for patent infringement, and the Canadian proceeding will not conclusively determine questions of patent infringement or invalidity, and Pfizer denies the remaining allegations contained in paragraph 13 of the Complaint.
- Pfizer admits that, by letter dated August 5, 2003 (a copy of which is attached to 14. as Exhibit C to the Complaint), Teva requested that Pfizer provide a covenant that Pfizer will not enforce the '889 and '489 patents against Teva, Teva requested a response within 45 days of receipt, and, having no obligation, Pfizer did not respond to the August 5, 2003 letter.

-2-NEWYORK 4220121 (283

- Pfizer admits that it or its affiliates are parties in the referenced actions and refers 15. to the respective complaints for the complete contents thereof, and denies the remaining allegations contained in paragraph 15 of the Complaint.
 - 16. Pfizer denies the allegations contained in paragraph 16 of the Complaint.
- 17. Pfizer admits that Teva filed this declaratory judgment action but denies the remaining allegations contained in paragraph 17 of the Complaint.
- Pfizer is without knowledge or information sufficient to form a belief as to the 18. truth of the allegations contained in paragraph 18 of the Complaint.
- 19. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 19 of the Complaint.
 - Pfizer denies the allegations contained in paragraph 20 of the Complaint. 20.
 - 21. Pfizer denies the allegations contained in paragraph 21 of the Complaint.
- 22. Pfizer denies that Teva is entitled to the relief sought in items A-F in the "Prayer for Relief' of the Complaint.

AFFIRMATIVE DEFENSES TO COMPLAINT

- The Court lacks subject matter jurisdiction over Teva's declaratory judgment 23. action.
- 24. Teva's Complaint is barred, in whole or in part, because it fails to state a claim upon which relief may be granted.

PRAYER FOR RELIEF REGARDING COMPLAINT

WHEREFORE, Pfizer respectfully requests that the Court enter an Order and Judgment:

- Dismissing Teva's Complaint with prejudice; A.
- Awarding to Pfizer its costs and attorneys' fees and expenses incurred in B.

-3-NEWYORK 4220121 (2K)

defending against Teva's Complaint; and

Awarding Pfizer such other and further relief as the Court deems just and proper. C.

COUNTERCLAIMS OF PFIZER INC.

In view of this Court's July 27, 2004 decision and accompanying Order, and contingent upon a final determination that this Court has subject matter jurisdiction over Teva's Complaint, defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, asserts the following compulsory counterclaims ("Counterclaims") against plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"):

THE PARTIES

- Pfizer Inc. is a corporation organized and existing under the laws of the State of ſ. Delaware, having a place of business at 235 East 42nd Street, New York, New York, 10017-5575.
- Upon information and belief, Teva Pharmaceuticals USA, Inc. is a corporation 2. organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.

JURISDICTION AND VENUE

- Pfizer's assertion of these Counterclaims is predicated upon this Court's July 27, 3. 2004 decision and accompanying Order. Nothing herein is intended to waive or detract from Pfizer's position that subject matter jurisdiction for the instant action is lacking.
- To the extent the Court has jurisdiction over Teva's declaratory judgment action, 4. this Court also has subject matter jurisdiction over these Counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338(a).
 - Teva is subject to personal jurisdiction in this judicial district. 5.

-4-NEWYORK 4220121 (2K)

Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b). 6.

Pfizer's Patents

- On February 25, 1997, the United States Patent and Trademark Office issued 7. United States Patent No. 5,605,889 (the "'889 patent"), entitled "Method of Administering Azithromycin." The '889 patent has been assigned to, and continues to be owned by, Pfizer.
- On July 31, 2001, the United States Patent and Trademark Office issued United States Patent No. 6,268,489 (the "'489 patent"), entitled "Azithromycin Dihydrate." The '489 patent has been assigned to, and continues to be owned by, Pfizer.

Zithromax®

- Pfizer holds approved New Drug Applications ("NDAs") for, among other dosage 9. forms, 250 mg and 600 mg azithromycin tablets (the "Zithromax® NDAs").
- Pfizer markets and sells its azithromycin products under the trade name 10. Zithromax®.

Teva's ANDAs

- Teva has represented that it submitted Abbreviated New Drug Application No. 11. 65-153 to the FDA pursuant to 21 U.S.C. §§ 355(j) (the "250 mg ANDA"), seeking approval to market 250 mg azithromycin tablets ("Teva's 250 mg Product").
- Teva has represented that it submitted Abbreviated New Drug Application No. 12. 65-150 to the FDA pursuant to 21 U.S.C. §§ 355(j) (the "600 mg ANDA," and together with the 250 mg ANDA, the "Teva ANDAs"), seeking approval to market 600 mg azithromycin tablets ("Teva's 600 mg Product," and together with Teva's 250 mg Product, the "Teva Products").
- Upon information and belief, the Teva ANDAs refer to and rely upon the 13. Zithromax® NDAs and purport to contain data showing bioequivalence of the Teva Product with

-5-NEWYORK 4220121 (2K)

Zithromax®.

14. On or about August 5, 2003, Teva sent to Pfizer a letter stating that Teva had filed the Teva ANDAs and that it was seeking approval to market the Teva Products prior to the expiration of the '889 and '489 patents.

FIRST COUNTERCLAIM - INFRINGEMENT OF U.S. PATENT NO. 5.605,889

- 15. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-14 of these Counterclaims.
- Teva has infringed the '889 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by 16. submitting to the FDA ANDA Nos. 65-150 and 65-153, which seek approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Products prior to the expiration of the '889 patent.
- 17. Upon information and belief, Teva has knowingly and willfully infringed the '889 patent.
- 18. Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '889 patent.

SECOND COUNTERCLAIM - INFRINGEMENT OF U.S. PATENT NO. 6,268,489

- 19. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-14 of these Counterclaims.
- 20. Teva has infringed the '489 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting to the FDA ANDA Nos. 65-150 and 65-153, which seek approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Products prior to the expiration of the '489 patent.
 - 21. Upon information and belief, Teva has knowingly and willfully infringed the '489

-6-NEWYORK 4220121 (2K)

patent.

Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '489 22. patent.

PRAYER FOR RELIEF REGARDING COUNTERCLAIMS

WHEREFORE, if this Court has subject matter jurisdiction over Teva's Complaint, Pfizer Inc. prays for a judgment in its favor and against Teva Pharmaceuticals USA, Inc., as follows:

- A. Entering judgment for Pfizer for infringement of U.S. Patent No. 5,605,889;
- B. Entering judgment for Pfizer for infringement of U.S. Patent No. 6,628,489;
- C. Entering preliminary and permanent injunctive relief enjoining Teva from making, using, selling, offering to sell, or importing the Teva Products described in ANDA Nos. 65-150 and 65-153 until after the expiration of the '889 patent;
- D. Entering preliminary and permanent injunctive relief enjoining Teya from making, using, selling, offering to sell, or importing the Teva Products described in ANDA Nos. 65-150 and 65-153 until after the expiration of the '489 patent;
- E. Determining that this is an exceptional case under 35 U.S.C. § 285 and awarding Pfizer its reasonable attorneys' fees, costs, and expenses; and

-7-NEWYOLK 4220121 (2E)

F. Awarding Pfizer such other and further relief as the Court deems just and proper.

Dated: August 23, 2004 New York, New York

Respectfully submitted,

WHITE & CASE LLP

Dimitrios T. Drivas (DD 8891) Jeffrey J. Oelke (JO 2534) Adam Gahtan (AG 8802)

Adam Gahtan (AG 8802)

Brendan G. Woodard (BW 6194)

1155 Avenue of the Americas

New York, New York 10036 Phone: (212) 819-8200 Facsimile: (212) 354-8113

Attorneys for Pfizer Inc.

NEWYORK 4220121 (2K) -8-

CERTIFICATE OF SERVICE

I hereby certify that on this 23rd day of August, 2004, I caused to be served true and correct copies of the foregoing Answer and Counterclaims of Pfizer Inc. by electronic mail and first-class mail upon counsel for plaintiff Teva Pharmaceuticals USA, Inc. as follows:

Elizabeth J. Holland KENYON & KENYON One Broadway New York, New York 10004-1050 Telephone: (212) 425-7200

Facsimile: (212) 425-5288 E-mail: eholland@kenyon.com

Adam Gahtan

EXHIBIT D

WHITE & CASE LLP
Dimitrios T. Drivas (DD 8891)
Jeffrey J. Oelke (JO 2534)
Adam Gahtan (AG 8802)
1155 Avenue of the Americas
New York, New York 10036
Phone: (212) 819-8200
Attorneys for Defendant Pfizer Inc.

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., Plaintiff,	
v. PFIZER INC.,) Civil Action No. 04-CV-4979 (LAP)
Defendant.))) _)

AMENDED ANSWER AND COUNTERCLAIMS OF PFIZER INC.

Defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, for its amended answer to the complaint for declaratory judgment ("Complaint") of plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), responds as follows:

- 1. Pfizer admits the allegations contained in paragraph 1 of the Complaint.
- 2. Pfizer admits the allegations contained in paragraph 2 of the Complaint.
- 3. Pfizer admits the allegations contained in paragraph 3 of the Complaint.
- 4. Pfizer admits the allegations contained in paragraph 4 of the Complaint.
- 5. Pfizer admits the allegations contained in paragraph 5 of the Complaint.

- 6. Pfizer admits that this Court has original jurisdiction over matters arising under 35 U.S.C. § 1 et seq., but denies that this Court has jurisdiction over the subject matter of this declaratory judgment action.
- 7. Pfizer admits that Teva filed this declaratory judgment action for noninfringement and invalidity but denies the remaining allegations contained in paragraph 7 of the Complaint.
 - 8. Pfizer admits the allegations contained in paragraph 8 of the Complaint.
 - 9. Pfizer admits the allegations contained in paragraph 9 of the Complaint.
 - 10. Pfizer admits the allegations contained in paragraph 10 of the Complaint.
- 11. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 11 of the Complaint.
- 12. Pfizer admits that United States Patents Nos. 5,605,889 (the "889 patent") and 6,268,489 (the "'489 patent") relate to azithromycin, denies that the phrase "contain claims directed to azithromycin" is an accurate description of the claims of the patents, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in paragraph 12 of the Complaint.
- 13. Pfizer admits that it has initiated proceedings in Canada under Canadian law against the Canadian Minister of Health and Novopharm, and other generic companies, regarding Notices of Allegation concerning the Canadian counterparts to Pfizer's '489 and '889 patents. Pfizer affirmatively states that such proceedings are not actions for patent infringement, and the Canadian proceedings will not conclusively determine questions of patent infringement or invalidity, and Pfizer denies the remaining allegations contained in paragraph 13 of the Complaint,

NEWYORK 4241729 (2K)

- Pfizer admits that, by letter dated August 5, 2003 (a copy of which is attached to 14. as Exhibit C to the Complaint), Teva purported to notify Pfizer that it submitted Abbreviated New Drug Applications Nos. 65-150 and 65-153 for generic azithromycin tablets to the United States Food and Drug Administration, requested that Pfizer provide a covenant that Pfizer will not enforce the '889 and '489 patents against Teva, and requested a response within 45 days of receipt, and that, having no obligation, Pfizer did not respond to the August 5, 2003 letter.
- Pfizer admits the allegations contained in paragraph 15 of the Complaint and adds 15. that the instant action is being consolidated with Civil Action No. 03-CV-7423 (LAP).
- 16. Pfizer admits that it or its affiliates are parties in the referenced actions and refers to the respective complaints for the complete contents thereof, and denies the remaining allegations contained in paragraph 16 of the Complaint.
 - 17. Pfizer denies the allegations contained in paragraph 17 of the Complaint.
- 18. Pfizer admits that Teva filed this declaratory judgment action but denies the remaining allegations contained in paragraph 18 of the Complaint.
- Pfizer is without knowledge or information sufficient to form a belief as to the 19. truth of the allegations contained in paragraph 19 of the Complaint.
- 20. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 20 of the Complaint.
 - 21. Pfizer denies the allegations contained in paragraph 21 of the Complaint.
 - 22. Pfizer denies the allegations contained in paragraph 22 of the Complaint.
- 23. Pfizer denies that Teva is entitled to the relief sought in items A-F in the "Prayer for Relief' of the Complaint.

NEWYORK 4241729 -3-

AFFIRMATIVE DEFENSES TO COMPLAINT

- 23. The Court lacks subject matter jurisdiction over Teva's declaratory judgment action.
- 24. Teva's Complaint is barred, in whole or in part, because it fails to state a claim upon which relief may be granted.

PRAYER FOR RELIEF REGARDING COMPLAINT

WHEREFORE, Pfizer respectfully requests that the Court enter an Order and Judgment:

- A. Dismissing Teva's Complaint with prejudice;
- B. Awarding to Pfizer its costs and attorneys' fees and expenses incurred in defending against Teva's Complaint; and
 - C. Awarding Pfizer such other and further relief as the Court deems just and proper.

COUNTERCLAIMS OF PFIZER INC.

In view of this Court's July 27, 2004 decision and accompanying Order, and contingent upon a final determination that this Court has subject matter jurisdiction over Teva's Complaint, defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, asserts the following compulsory counterclaims ("Counterclaims") against plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"):

THE PARTIES

- 1. Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York, 10017-5575.
- 2. Upon information and belief, Teva Pharmaceuticals USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of

NEWYORK 4241729 (2K) 4 business at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.

JURISDICTION AND VENUE

- 3. Pfizer's assertion of these Counterclaims is predicated upon this Court's July 27, 2004 decision and accompanying Order. Nothing herein is intended to waive or detract from Pfizer's position that subject matter jurisdiction for the instant action is lacking.
- To the extent the Court has jurisdiction over Teva's declaratory judgment action, 4. this Court also has subject matter jurisdiction over these Counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338(a).
 - 5. Teva is subject to personal jurisdiction in this judicial district.
 - 6. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Pfizer's Patents

- 7. On February 25, 1997, the United States Patent and Trademark Office issued United States Patent No. 5,605,889 (the "'889 patent"), entitled "Method of Administering Azithromycin." The '889 patent has been assigned to, and continues to be owned by, Pfizer.
- 8. On July 31, 2001, the United States Patent and Trademark Office issued United States Patent No. 6,268,489 (the "489 patent"), entitled "Azithromycin Dihydrate." The '489 patent has been assigned to, and continues to be owned by, Pfizer.

Zithromax®

- 9. Pfizer holds an approved New Drug Application ("NDA") for, among other dosage forms, 500 mg azithromycin tablets (the "Zithromax® NDA").
- 10. Pfizer markets and sells its azithromycin products under the trade name Zithromax®.

NEWYORK 4241729

Teva's ANDA

- Teva has represented that it submitted Abbreviated New Drug Application No. 11. 65-193 to the FDA pursuant to 21 U.S.C. §§ 355(j) (the "Teva ANDA"), seeking approval to market 500 mg azithromycin tablets (the "Teva Product").
- 12. Upon information and belief, the Teva ANDA refers to and relies upon the Zithromax® NDA and purports to contain data showing bioequivalence of the Teva Product with Zithromax®.
- 13. On or about August 5, 2003, Teva sent to Pfizer a letter stating that Teva had filed ANDAs with respect to azithromycin and that it was seeking approval to market its azithromycin products prior to the expiration of the '889 and '489 patents.

FIRST COUNTERCLAIM - INFRINGEMENT OF U.S. PATENT NO. 5,605,889

- 14. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-13 of these Counterclaims.
- 15. Teva has infringed the '889 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting to the FDA ANDA No. 65-193, which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Product prior to the expiration of the '889 patent.
- 16. Upon information and belief, Teva has knowingly and willfully infringed the '889 patent.
- 17. Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '889 patent.

SECOND COUNTERCLAIM - INFRINGEMENT OF U.S. PATENT NO. 6,268,489

18. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-13 of these Counterclaims.

- Teva has infringed the '489 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by 19. submitting to the FDA ANDA No. 65-193, which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Product prior to the expiration of the '489 patent.
- Upon information and belief, Teva has knowingly and willfully infringed the '489 20. patent.
- Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '489 21. patent.

PRAYER FOR RELIEF REGARDING COUNTERCLAIMS

WHEREFORE, if this Court has subject matter jurisdiction over Teva's Complaint, Pfizer Inc. prays for a judgment in its favor and against Teva Pharmaceuticals USA, Inc., as follows:

- A. Entering judgment for Pfizer for infringement of U.S. Patent No. 5,605,889;
- В. Entering judgment for Pfizer for infringement of U.S. Patent No. 6,628,489;
- C. Entering preliminary and permanent injunctive relief enjoining Teva from making, using, selling, offering to sell, or importing the Teva Product described in ANDA No. 65-193 until after the expiration of the '889 patent;
- Entering preliminary and permanent injunctive relief enjoining Teva from D. making, using, selling, offering to sell, or importing the Teva Products described in ANDA No. 65-193 until after the expiration of the '489 patent;
- Determining that this is an exceptional case under 35 U.S.C. § 285 and awarding E. Pfizer its reasonable attorneys' fees, costs, and expenses; and

NEWYORK 4241729 (280)

F. Awarding Pfizer such other and further relief as the Court deems just and proper.

Dated: August 27, 2004 New York, New York

Respectfully submitted,

WHITE & CASE LLP

Dimitrios T. Drivas (DD 8891)
Jeffrey J. Oelke (JO 2534)
Adam Gahtan (AG 8802)

Brendan G. Woodard (BW 6194) 1155 Avenue of the Americas New York, New York 10036

Phone: (212) 819-8200 Facsimile: (212) 354-8113

Attorneys for Pfizer Inc.

CERTIFICATE OF SERVICE

I hereby certify that on this 27th day of August, 2004, I caused to be served true and correct copies of the foregoing Amended Answer and Counterclaims of Pfizer Inc. by electronic mail and first-class mail upon counsel for plaintiff Teva Pharmaceuticals USA, Inc. as follows:

Elizabeth J. Holland KENYON & KENYON One Broadway New York, New York 10004-1050 Telephone: (212) 425-7200 Facsimile: (212) 425-5288

E-mail: eholland@kenyon.com

Adam Gahtan

EXHIBIT E



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: CURATOLO, ET AL.

Examiner: Elli Peselev

APPLICATION NO.: 11/041,194

Group Art Unit: 1623

FILING DATE: January 20, 2005

TITLE: METHOD OF ADMINISTERING

AZITHROMYCIN

Commissioner for Patents Mail Stop Reissue P.O. Box 1450 Alexandria, VA 22313-1450

Sir.

AMENDMENT AND RESPONSE TO OFFICE ACTION

This is in response to the Examiner's Office Action, dated July 18, 2005, for the above referenced patent application. Applicants kindly request entry of the present amendments and consideration of the remarks herein, which are respectfully presented to place the application in condition for allowance.

Please amend the claims in accordance with the claim listing, which begins at page 2 of this paper.

- 92. (Original) A method as defined in claim 83, wherein said dosage form is in the form of a unit dose packet.
- 93. (Original) A method as defined in claim 92, wherein said dosage form is in the form of a suspension made from said unit dose packet.

Please add new claim.

100. (New) A method as defined in claim 81, wherein said mammal has eaten food of any sort within 30 minutes prior to dosing azithromycin.

Remarks

Entry of the above amendments to the claims and addition of new claim 100 is respectfully requested. A separate paper is attached hereto that details the status of the claims and sets forth the support for the changes to the claims.

I. Background

The Zithromax® 250mg capsule was first approved in the United States and it was the first azithromycin dosage form marketed anywhere in the world. The Food and Drug Administration (FDA) approved the capsule on November 1, 1991, and Pfizer formally launched the product in March of 1992. The capsules were subsequently approved for commercial distribution in a number of countries around the world. All commercially distributed capsules contained azithromycin dihydrate as the specific polymorph of azithromycin.

In early development of Zithromax[®], Pfizer scientists conducted a food effect study using the non-stochiometric hydrate form of azithromycin in a standard hard gelatin capsule. It was observed that this capsule dosage form exhibited a significant adverse food effect, i.e., a significant loss in bioavailability when dosed with food. As a result, Phase III studies were conducted with dosing only in the fasted state. The FDA recognized the food effect limitation with language in the package insert directing patients to take capsules "one hour before or two hours after a meal", i.e., on an empty stomach.

In 1992, Pfizer launched tablet and oral suspension formulations of azithromycin dihydrate in Italy, with the same package insert as the capsules sold in the U.S. (dosed in fasted state), it being widely believed, at the time, that the food effect was more likely related to the azithromycin drug substance itself, as opposed to a particular dosage form.

In 1993, it was observed that the Zithromax[®] tablet formulation was superior to the capsule formulation in that the tablet had no appreciable food effect.

On April 29, 1994, a patent application, issuing as the '889 patent, was filed directed to specific oral dosage forms, to a therapeutic package, and to methods of treatment comprising dosing azithromycin in the "fed" state.

The FDA approved the Zithromax[®] 250mg tablet for U.S. distribution on July 18, 1996, and Pfizer formally launched the tablet in April of 1997. All commercially distributed tablets contained azithromycin dihydrate as the specific polymorph of azithromycin. As part of the original Zithromax[®] tablet new drug application (NDA), Pfizer demonstrated

bioequivalence between the tablet and the capsule in the fasted state. Pfizer also demonstrated that the tablet had no adverse food effect. As a result, the FDA granted approval for Zithromax[®] tablets with a labeling statement indicating that the tablets "may be taken with or without food."

II. <u>Discussion</u>

United States Patent 5,605,889 issued February 25, 1997. Based upon Pfizer's launch of tablet and oral suspension formulations of azithromycin dihydrate in Italy (1992), applicants have (a) deleted dosage form claims 1-74 and package claims 75-80 and 94-99 and (b) narrowed the breadth of method of treatment claims 81-93 (see appendix A) pursuant to 35 USC §251.

Independent claim 81 and claims 82-93 dependent therefrom, refer to a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin.

Support for narrowing the definition of "eaten" can be found in Examples 4-7 of the '889 patent. In each example, azithromycin is dosed to two (2) patient control groups: (a) first group — subjects who were dosed after an overnight fast of 10-12 hours and (b) second group — subjects who were dosed after consumption of either a high fat or low fat meal. There are no examples describing a control group dosing in the fasted state and consuming a meal post-dose. As a result, the '889 disclosure conveys the requisite "blaze marks" directing the skilled artisan to distinguish the narrower definition of "eaten" (patients who eat food of any sort within one hour prior to dosing) over the broader original definition, Purdue Pharma L.P. v. Faulding, Inc., 2000 U.S. App. Lexis 26797 (Fed Cir. 2000).

Pursuant to 37 C.F.R. §1.178(b) applicants apprise the Office that the United States Patent No. 5,605,889 (the '889 patent) was the subject of Civil Action Nos. 03-7423 (IAP) and 04-4979 (IAP), resulting from a complaint filed by Teva Pharmaceuticals USA, Inc. ("Teva"). On December 21, 2004, Pfizer unconditionally agreed not to enforce the '889 patent against Teva or any Teva affiliate, for having made, making, using, offering for sale, selling, or importing the azithromycin tablets as described in Teva's ANDA Nos. 65-150, 65-153 and 65-193.

The Examiner has rejected claims 81-93 and 100, under 35 U.S.C. 251, as being based upon a defective reissue declaration. The Examiner states that the reissue oath/declaration filed with this application is defective because it fails to identify at least one

error which is relied upon to support the reissue application. See 37 CFR 1.175 (a)(1) and MPEP §1414. The declaration states that claims 81-93, as issued, are described in the prior art, however, said prior art has not been identified and no reason is provided for the cancellation of all the other claims.

Applicants respectfully submit that the filing of a new declaration, herewith, identifying the prior art as the Zithromax (Trademark of Pfizer Inc.) Tablet and Powder for Oral Suspension Package Insert for azithromycin tablets and powder for oral suspension dosage forms sold commercially in Italy (1992).

The Examiner further states that the reissue oath/declaration filed with this application is defective because it fails to contain a statement that all errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant (see 37 CFR 1.175 and MPEP§ 1414).

Applicants respectfully submit on page 2 of the declaration a statement that: "All errors corrected in this reissue application arose without any deceptive intention on the part of the application."

Lastly, applicants file herewith a Supplemental Information Disclosure Statement pursuant to 37 CFR 1.56.

Applicants believe that, in view of the amendments and remarks made above, this application is in condition for allowance.

Date: AUGUST 25, 2005

B. Timothy Creagan
Attorney for Applicant(s)

Reg. No. 39,156

Pfizer Inc Patent Department Eastern Point Road, MS8260-1611 Groton, Connecticut 06340 (860) 715-4546

Status of claims and Support for Claim Changes

Claim Number(s)	Status of Claim	Support for Claim Changes
1-80	Cancelled	
81	Pending (Amended)	Column 3, lines 3-6; and Examples 4-7
82	Pending	
83	Pending	
84	Pending	
85	Pending	
86	Pending	
87	Pending	
88	Pending	
89	Pending	·
90	Pending (Amended)	Original claim; correction of dependency
91	Pending	
92	Pending	
93	Pending	
94-99	Cancelled	
100	New	Example 5, particularly, column 14, lines 4-8

EXHIBIT F

02/17/06 16:54 FAX JUDGE PRESKA 2002/002

UNITED STATES DISTRICT COURT SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS

Plaintiff,

03 Civ. 7423(LAP) & 04 Civ. 4979 (LAP)

v.

MEMORANDUM AND ORDER

PFIZER, INC.,

USA, INC.

Defendant.

_____x

LORETTA A. PRESKA, United States District Judge:

In light of Pfizer's granting to Teva a covenant not to sue with respect to the '489 patent, the parties' motions for discovery and summary judgment (docket nos. 35 and 37) are denied as moot.

The parties shall confer and inform the court of the proposed briefing schedule on Teva's motion for attorney's fees. To the extent that Teva wishes to brief the unenforceability issue in connection with its attorney's fees motion, it may do so by reference to arguments made in papers submitted on the summary judgment motions. Pfizer may respond in like fashion in its opposition papers.

SO ORDERED

February 17, 2006

Loretta A. Preska, U.S.D.J.

EXHIBIT G

6 DRT CV 1134 IN THE UNITED STATES DISTRICT FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.

Plaintiffs,

٧.

Civil Action No.

PFIZER INC.,

Defendant.

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd."), for their Complaint against Pfizer Inc. ("Pfizer"), allege on personal belief as to themselves and on information and belief as to the conduct of Pfizer as follows:

THE PARTIES

- Teva USA is a Delaware corporation with its principal place of business 1. located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.
- Teva Ltd. is a corporation organized under the laws of Israel, and 2. maintains its principal place of business at 5 Basel Street, Petach Tikva 49131, Israel.
- On information and belief, Pfizer is a Delaware corporation with its 3. principal place of business at 235 East 42nd Street, New York, New York, 10017-5575.

- On information and belief, Pfizer owns U.S. Patent No. 6,977,243 ("the 4. '243 patent"), entitled "Crystal Forms of Azithromycin," a copy of which is attached hereto as Exhibit A.
- 5. On information and belief, Pfizer holds New Drug Application ("NDA") No. 50-711 for ZITHROMAX® 250 mg azithromycin tablets, NDA No. 50-730 for ZITHROMAX[®] 600 mg azithromycin tablets; and NDA No. 50-784 for ZITHROMAX[®] 500 mg azithromycin tablets.

JURISDICTION AND VENUE

- 6. This Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 et seq.
- 7. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction seeking a declaratory judgment that the '243 patent is invalid and not infringed.
- 8. Personal jurisdiction exists over the defendant because defendant has its principal place of business within this district, and because defendant does business within this district.
 - 9. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and 1400(b).

THE PRESENCE OF AN ACTUAL CONTROVERSY

- 10. Teva USA holds Abbreviated New Drug Application ("ANDA")

 Number 65-153 for 250 mg azithromycin tablets; ANDA Number 65-150 for 600 mg

 azithromycin tablets and ANDA No. 65-193 for 500 mg azithromycin tablets.
- 11. On November 14, 2005, the United States Food and Drug

 Administration ("FDA") granted Teva USA approval to market 250 mg, 500 mg, and 600 mg

 azithromycin tablets pursuant to its ANDAs. Teva USA began marketing its 250 mg, 500 mg,

 and 600 mg azithromycin tablets on or about that date.
- 12. The active pharmaceutical ingredient ("API") in Teva USA's azithromycin tablets is azithromycin monohydrate hemiethanolate (the "hemiethanolate"). The hemiethanolate is a unique crystalline form of azithromycin, which has been patented by Teva Ltd.
- 13. Pfizer's '243 patent contains claims to azithromycin sesquihydrate (the "sesquihydrate"), which is a crystalline form of azithromycin different from the hemiethanolate.
- 14. Pfizer has demonstrated its intention to enforce the '243 patent against Teva USA and Teva Ltd. In particular, notwithstanding the fact that the API in Teva USA's azithromycin tablets is not the sesquihydrate, Pfizer has brought suit against Teva USA and Teva Ltd. in the District of Delaware claiming that Teva USA has been and is infringing the '243 patent by importing into the United States and selling and offering to sell within the United States its azithromycin tablets and that Teva Ltd. has actively induced Teva USA to infringe the '243 patent.

- 15. Pfizer has previously claimed that Teva USA's azithromycin tablets infringe one of its patents. In Teva Pharmaceuticals USA, Inc. v. Pfizer, Inc., 03cv7423 and 04cv4979 (LAP) (consolidated), currently pending before this Court, Teva USA seeks a declaratory judgment that its azithromycin tablets do not infringe Pfizer's U.S. Patent No. 6,268,489 (the "'489 patent"), and that the '489 patent is invalid and unenforceable. The '489 patent claims "crystalline azithromycin dihydrate" ("dihydrate"), another crystalline form of azithromycin different from the hemiethanolate. Pfizer counterclaimed against Teva USA, alleging that Teva USA's sale of its azithromycin tablets would infringe the '489 patent.
- 16. Pfizer (or its predecessor) has also demonstrated its intention to protect other products from generic competition by Teva USA. On at least five occasions, Pfizer sued or maintained suit against Teva USA (or its related entities) for patent infringement relating to other drugs for which Teva USA has filed an ANDA: (i) Pfizer Inc. and Pfizer Technologies Ltd. v. Novopharm Ltd., 00-cv-01475 (N.D. Ill.), concerning fluconazole; (ii) Pfizer Inc./Warner-Lambert v. Teva, 00-cv-4589 and 00-cv-4168 (D.N.J.), concerning gabapentin; (iii) Schwarz Pharma, Inc., Schwarz Pharma AG and Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc., 01-cv-4995 (D.N.J.), concerning moexipril; (iv) Bayer and Pfizer v. Biovail & Teva, 01-cv-1205 and 01-cv-1206 (D.P.R.), concerning nifedipine; and (v) Warner-Lambert v. Teva USA, 99cv-0922 (D.N.J.), concerning quinipril.
- 17. Based on the above, an actual controversy exists between Teva USA, Teva Ltd. and Pfizer with respect to the '243 patent and Teva USA's 250 mg, 500 mg and 600 mg azithromycin tablets.

COUNT I DECLARATORY JUDGMENT OF NONINFRINGEMENT

- 18. The allegations of Paragraphs 1 to 17 are incorporated by reference as if fully set forth herein.
- 19. Teva USA's manufacture, use, offer for sale, sale, and/or importation of its 250 mg, 500 mg and 600 mg azithromycin tablets pursuant to ANDA Nos. 65-153, 65-193 and 65-150, respectively, has not infringed and does not infringe any valid and properly construed claim of the '243 patent.

COUNT II DECLARATORY JUDGMENT OF NONINFRINGEMENT

- 20. The allegations of Paragraphs 1 to 19 are incorporated by reference as if fully set forth herein.
- 21. Teva Ltd. has not and is not actively inducing Teva USA to infringe any valid and properly construed claim of the '243 patent.

COUNT II DECLARATORY JUDGMENT OF PATENT INVALIDITY

- 22. The allegations of Paragraphs 1 to 21 are incorporated by reference as if fully set forth herein.
- The claims of the '243 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

PRAYER FOR RELIEF

WHEREFORE, Teva USA and Teva Ltd. respectfully request the Court enter judgment against Pfizer to include:

- A. A declaration that Teva USA's manufacture, use, importation, offer for sale or sale of Teva's azithromycin products pursuant to ANDA Nos. 65-153, 65-150, and 65-193 has not infringed and does not infringe any claim of United States Patent No. 6,977,243;
- B. A declaration that Teva Ltd. has not directly or indirectly infringed, and is not directly or indirectly infringing, any claim of United States Patent No. 6,977,243;
 - C. A declaration that United States Patent No. 6,977,243 is invalid;
- D. An award to Teva USA and Teva Ltd. of their reasonable costs and attorneys' fees in connection with this action;
- E. An injunction prohibiting Pfizer and its officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, from threatening or charging infringement of, or instituting or maintaining any action for infringement of U.S. Pat. No. 6,977,243 against Teva USA or Teva Ltd., and
 - F. Such other and further relief as the Court may deem just and proper.

Respectfully submitted,

KENYON & KENYON LLP

Dated: February 14, 2006

Steven J. Lee (SL1043)

By:

Elizabeth J. Holland (EH0850)

Sheila Mortazavi (SM3665)

Cynthia Lambert Hardman (CH2281)

One Broadway

New York, NY 10004

Tel.: (212) 425-7200

Fax: (212) 425-5288 Counsel for Plaintiffs, TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.

EXHIBIT A

US006977243B2

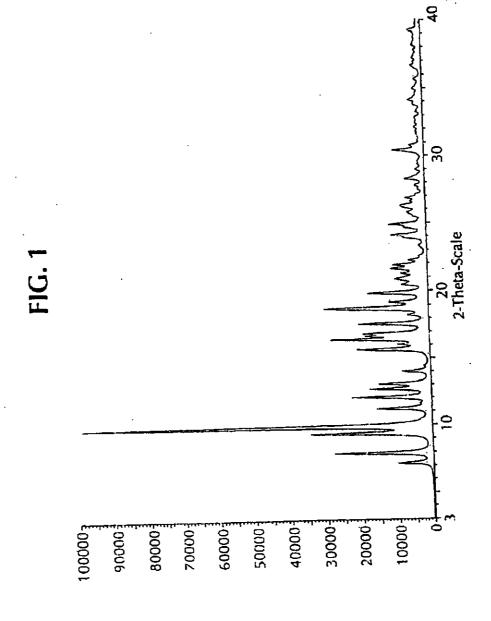
(12) United States Patent Li et al.

(10) Patent No.: (45) Date of Patent:

US 6,977,243 B2 at: *Dec. 20, 2005

		FORMS OF AZITHROMYCIN	6,52	8,492 B1 3/2003	de la Torre Garcia	
(54)	CKARIAI	LOKAR OF YMITHKORIT 4-			et al	
/mm	T	Zheng J. Li, Quaker Hill, CT (US);			Arophime et al.	
(75)	Inventors:	Andrew V. Trask, Stonington, CT (US)			Rengaraju	
		William At It mind committee (2002/01			
(73)	Assignce: Pfizer Inc., New York, NY (US) FOREIGN PATENT DOCUMENT					
		Subject to any disclaimer, the term of this	CA	2245398	2/2000C07H/17/00	
(*)	Notice:	patent is extended or adjusted under 35	CN	1093370	12/1994 C07H/17/08	
		U.S.C. 154(b) by 0 days.	CN	111 49 60	1/1996 C07H/17/08	
		0.3.C. 134(0) by 6 0232	CN	1161971	10/1997 C07H/17/08	
			EP	0298650	6/1988	
		This patent is subject to a terminal dis-	HP	0941999	9/1999 C07H/17/08 2/2000 C07H/17/08	
		claimer.	距	1103558	5/2001 C071H/17/08	
			EP .	1103558 1234833	8/2002 C07H/17/08	
(21)	Appl. No.	: 10/152,106	EP	WO 9804574	2/1998 C07H/17/06	
(21)	t the rece		₩O	WO 0014099	3/2000 C0/H/17/08	
(22)	Filed:	May 21, 2002	WO	WO 003Z203	6/2000 A61K/31/70	
		Prior Publication Data	₩O	WO 0100640	1/2001 C07H/17/08	
(65)			wo	WO 0149697	7/2001 C07H/1/00	
	US 2003/0	162730 Al Aug. 28, 2003	WO	WO 0187912	11/2001 C07H/17/08	
			WO	WO 0207736	1/2002 A61K/31/7048	
	Re	lated U.S. Application Data	WO	₩O 0209640	2/2002	
(60)	D-11-1-1-1	Lauration No. 60/292-565, filed on May 24,	WO	WO 0210181	2/2002 C07H/17/08	
(/	AAA4	Lives workering No. 01/29/-/41, 1100 01 744.	WO	WO 0215842	2/2002	
	12, 2001, 1	red Dighteloug abblication (see only abloar) men	WO	WO 0242315	5/2002	
	on Dec. 21	, 2001.	wo	WO 02085898	10/2002 C07D/413/14 11/2002 C07H/17/08	
		A CATE 21 PM. COTE 17/08	WO	WO 0187912	4/2003	
(51)	Int. Cl.	A61K 31/70, C07H 17/08	WO	WO 03032922	7/2005	
(52)	U.S. Cl.	514/29; 536/7.4	OTHER PUBLICATIONS			
()			Chemic	al Abstracts, vol. 12	4, No. 3 (Jan. 15, 1996) Abstract	
(58)	Field of	Search 514/29; 536/7.4	No. 29525, Abstract of CN1093370.			
(56)		References Cited	• cited by examiner			
	τ	U.S. PATENT DOCUMENTS		Prominer Tilli D	aceleu	
		A 5/1982 Kobrehel et al 536/7.4	Primary Examiner—Elli Pesclev (74) Auorney, Agent, or Firm—Gregg C. Benson; B. Timothy Creagan; Lance Y. Liu			
	4,328,334					
	4,465,674	174 710)				
	4,517,359 A 5/1985 Kobrehel et al		(57)	(57) ABSTRACT		
			• '	(81)		
			The invention relates to crystal forms of azithromycin, an			
			antibio	antibiotic useful in the treatment of infectious.		
			24 Claims, 33 Drawing Sheets			
	6,451,990			4. C.		

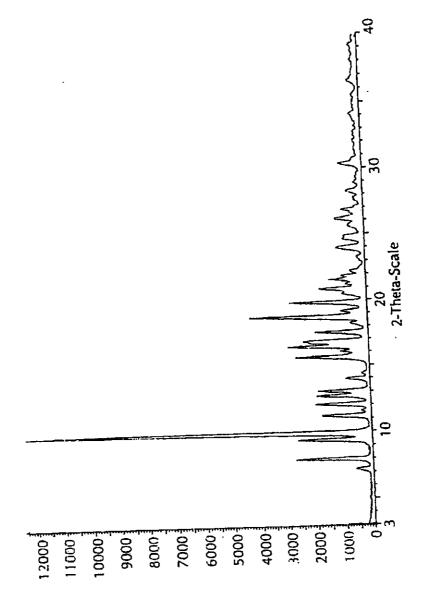
U.S. Patent Dec. 20, 2005 Sheet 1 of 33



U.S. Patent Dec. 20, 2005

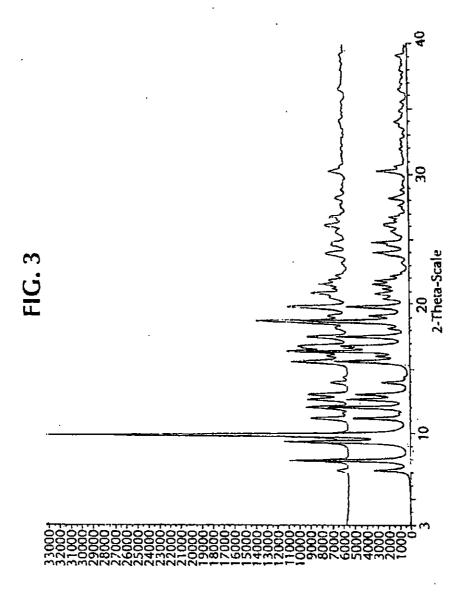
Sheet 2 of 33





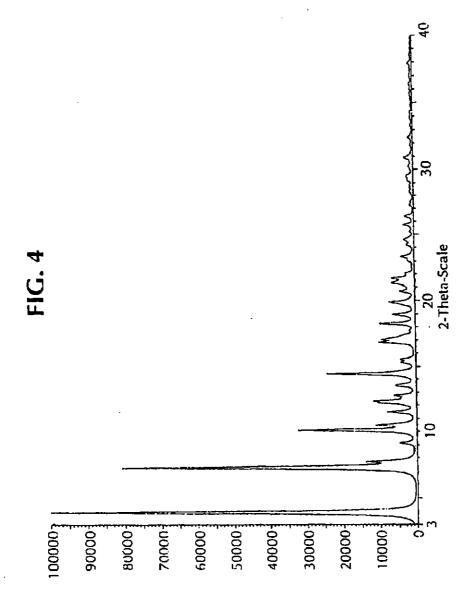
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Sheet 3 of 33

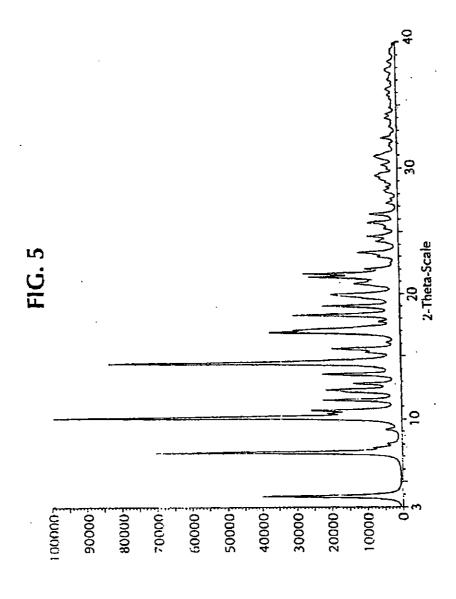


Dec. 20, 2005

Sheet 4 of 33

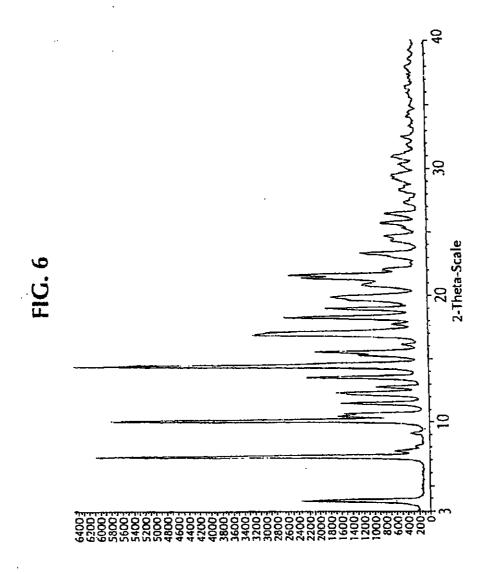


Dec. 20, 2005 Sheet 5 of 33 US 6,977,243 B2



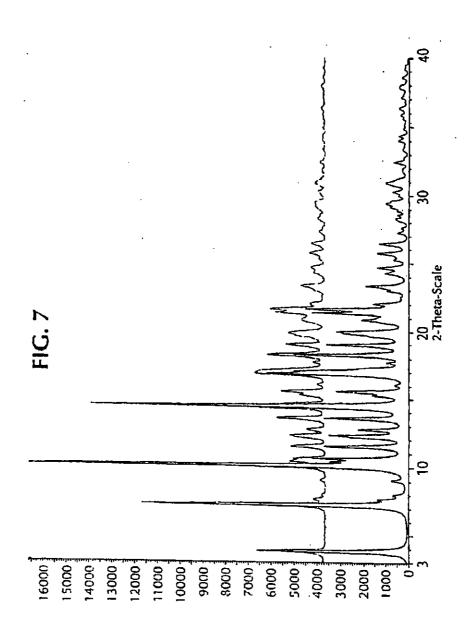
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Sheet 6 of 33 US 6,977,243 B2



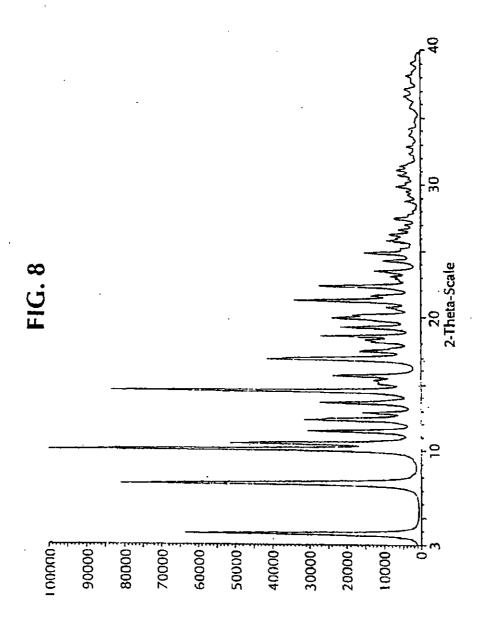
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Sheet 7 of 33



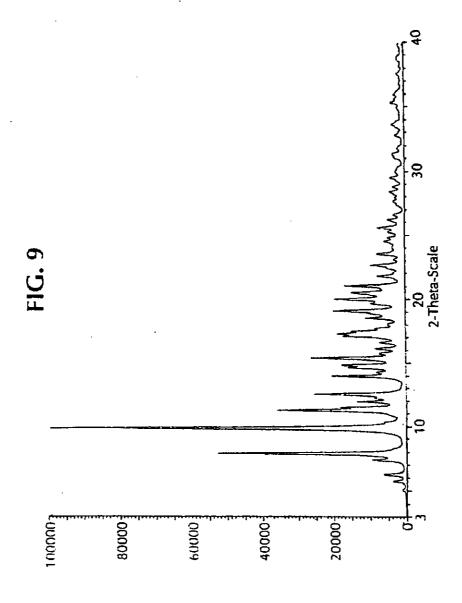
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Sheet 8 of 33

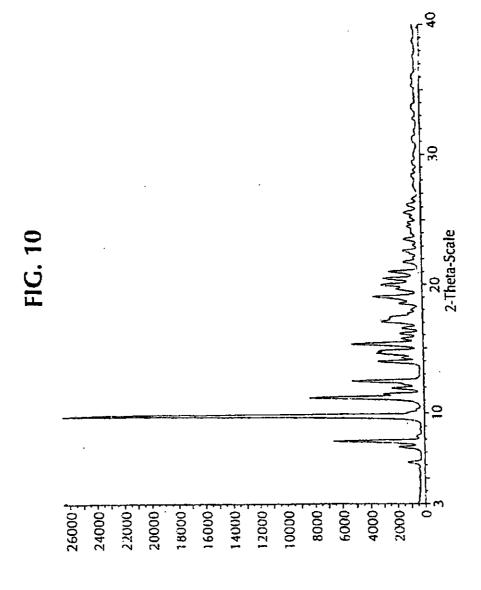


U.S. Patent Dec. 20, 2005

Sheet 9 of 33

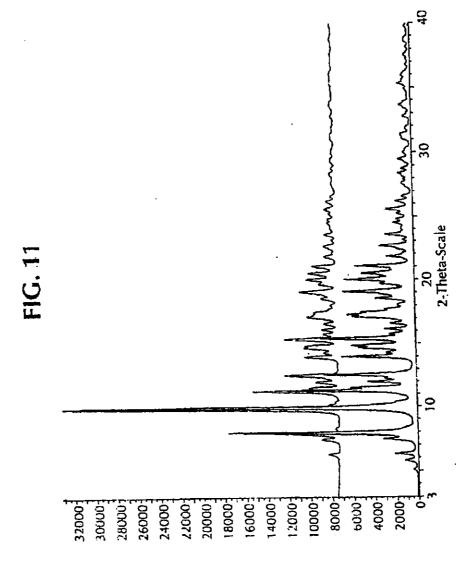


Dec. 20, 2005 Sheet 10 of 33 US 6,977,243 B2



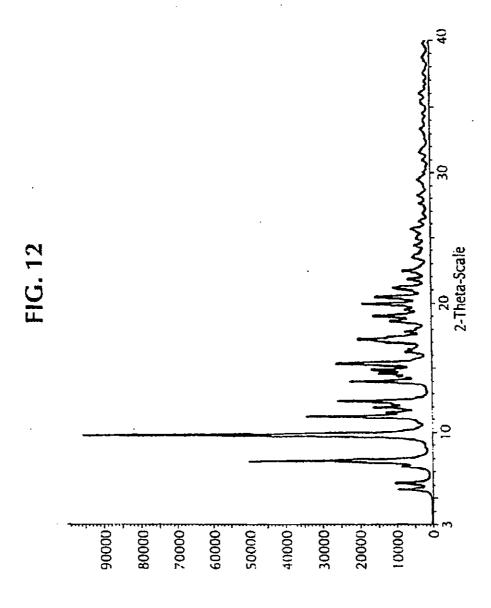
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Sheet 11 of 33



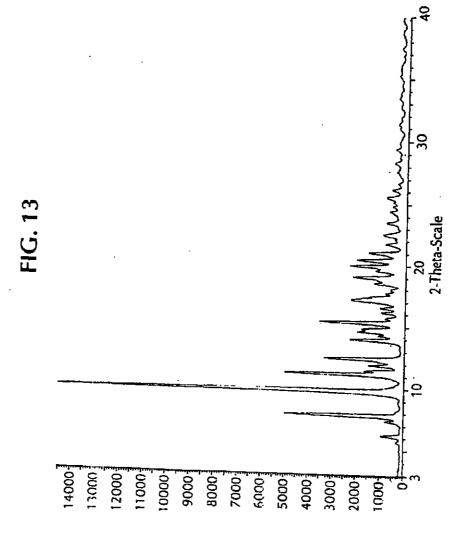
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Sheet 12 of 33



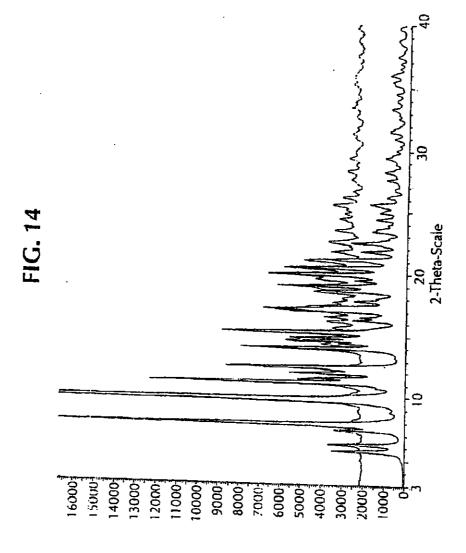
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Sheet 13 of 33



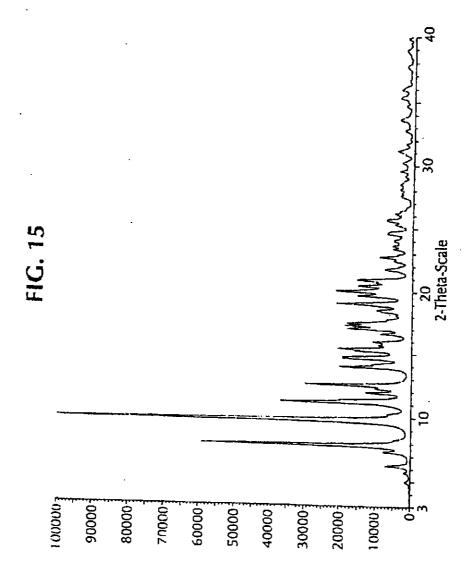
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Sheet 14 of 33



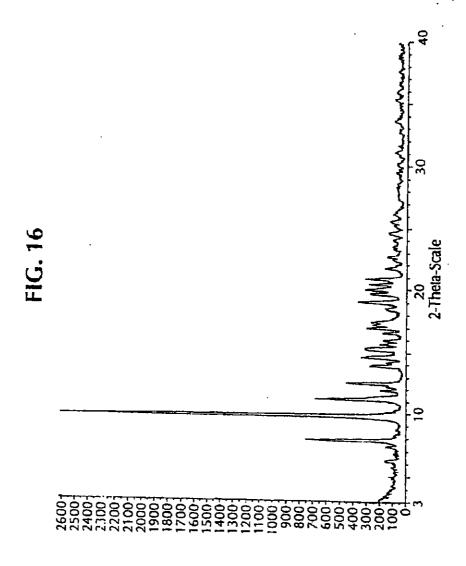
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Sheet 15 of 33



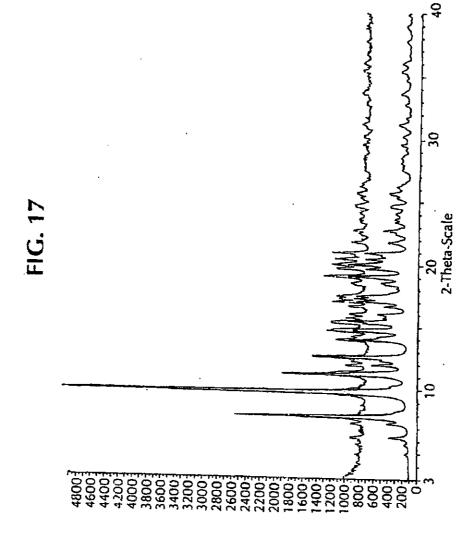
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Sheet 16 of 33



Dec. 20, 2005

Sheet 17 of 33

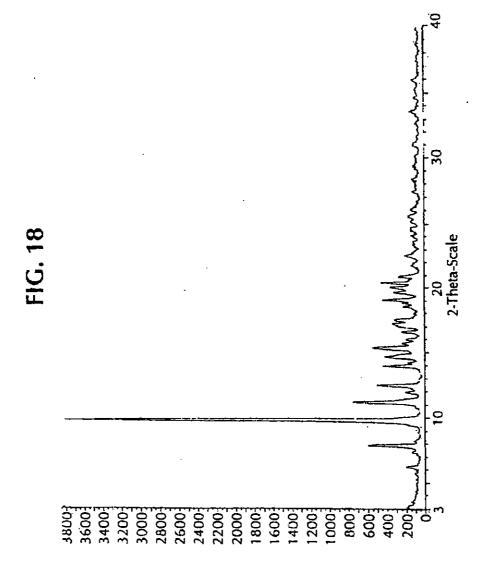


U.S. Patent

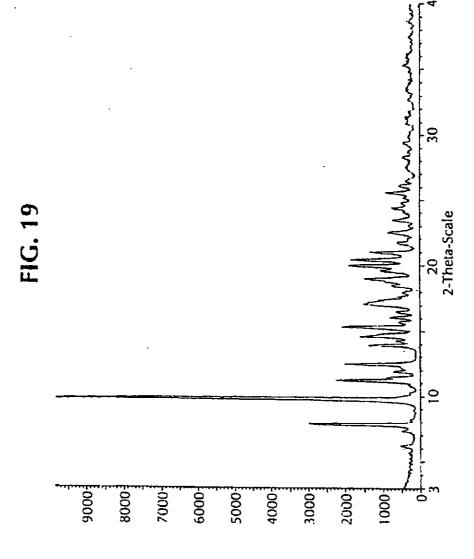
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Sheet 18 of 33

US 6,977,243 B2

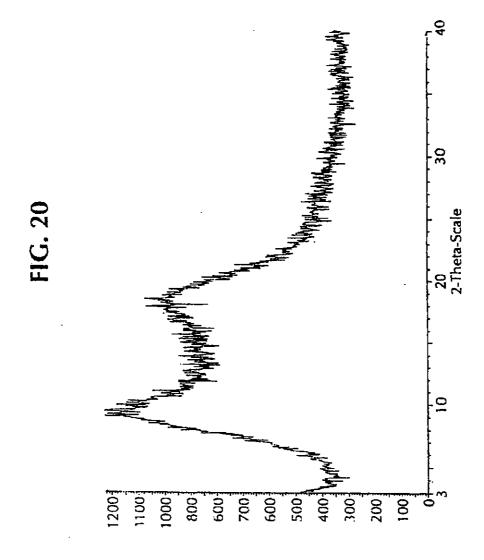


U.S. Patent Dec. 20, 2005 Sheet 19 of 33 US 6,977,243 B2



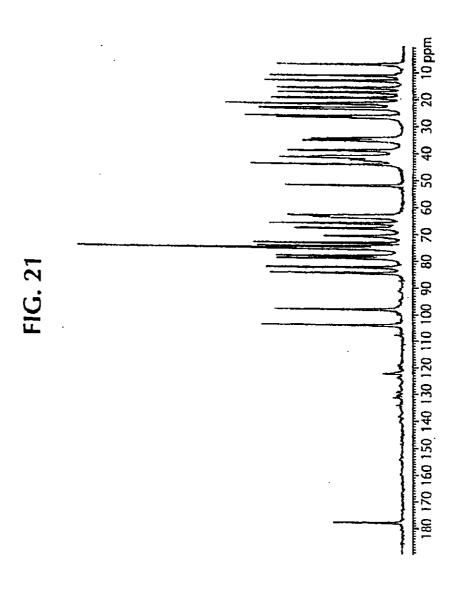
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Sheet 20 of 33



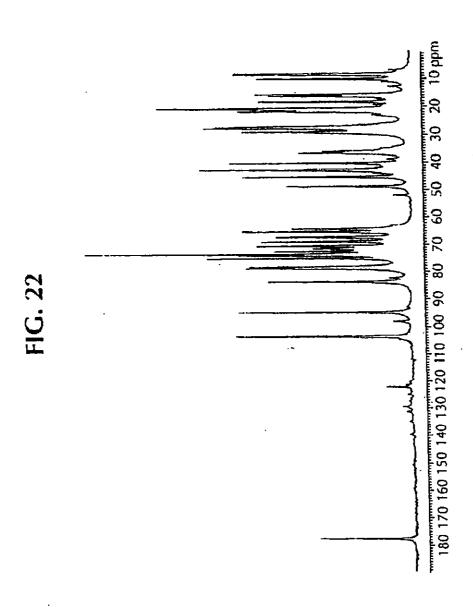
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Sheet 21 of 33

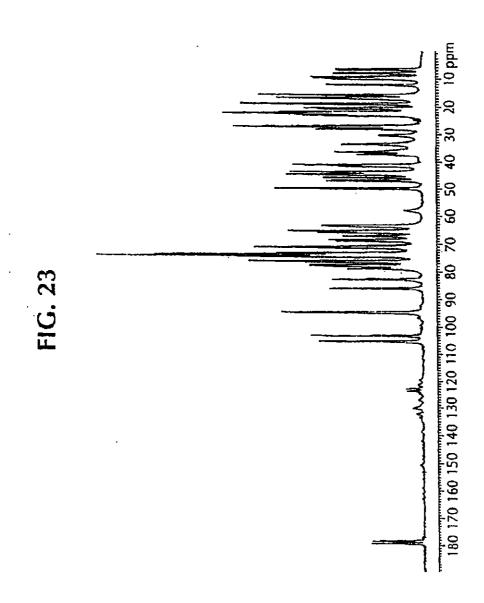


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Sheet 22 of 33

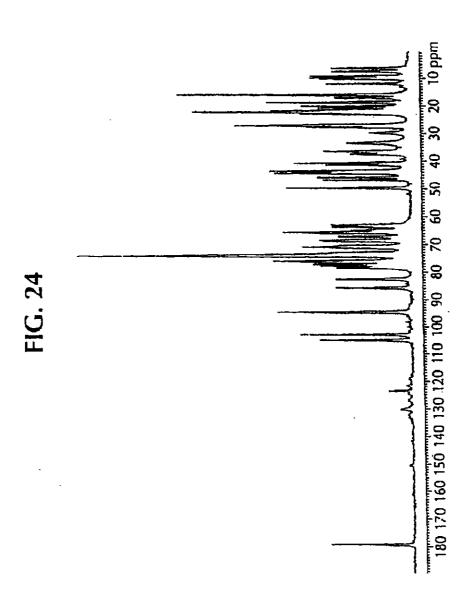


U.S. Patent Dec. 20, 2005 Sheet 23 of 33



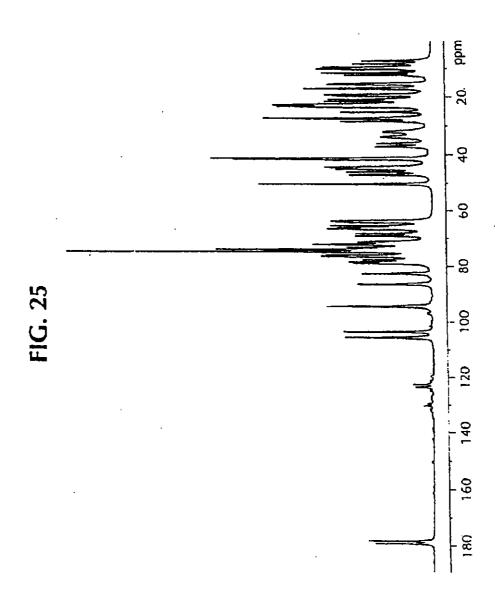
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Sheet 24 of 33

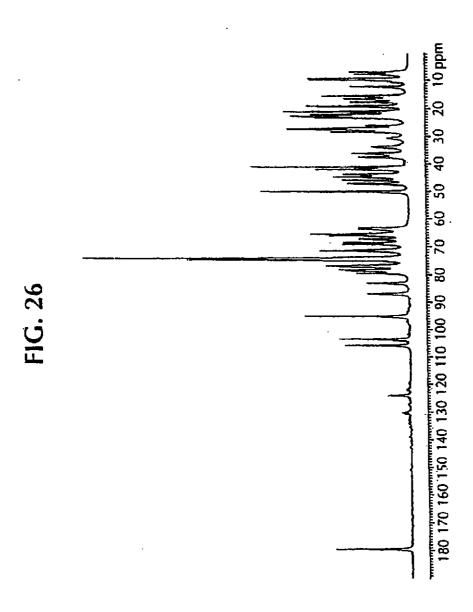


U.S. Patent Dec. 20, 2005

Sheet 25 of 33 US 6,977,243 B2

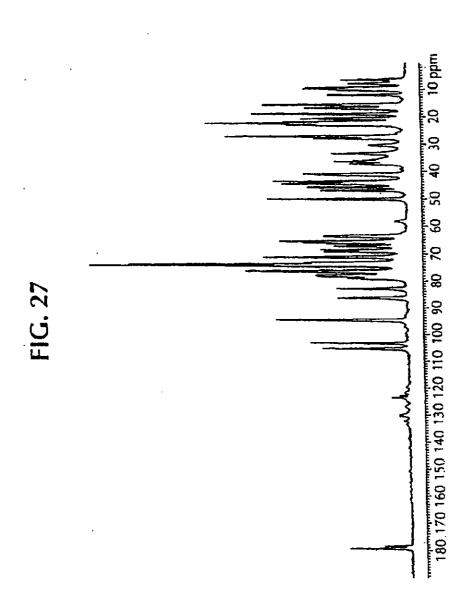


U.S. Patent Dec. 20, 2005 Sheet 26 of 33



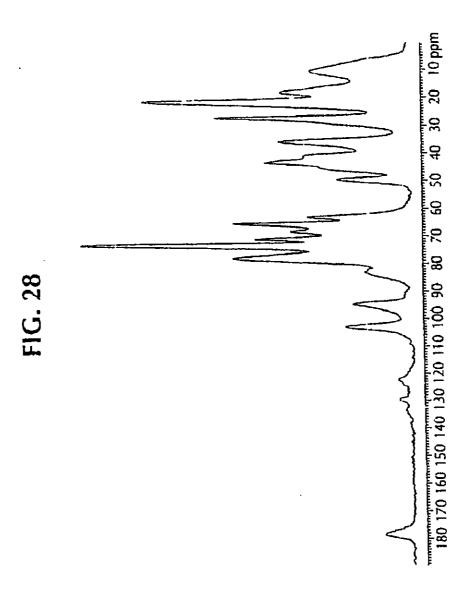
Dec. 20, 2005

Sheet 27 of 33

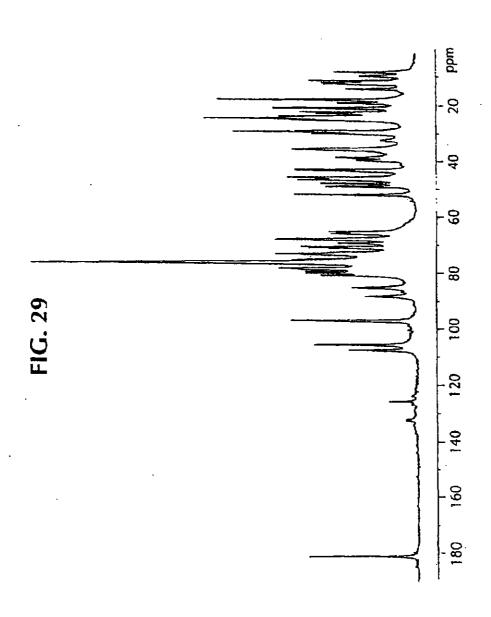


U.S. Patent Dec. 20, 2005

Sheet 28 of 33



U.S. Patent Dec. 20, 2005 Sheet 29 of 33

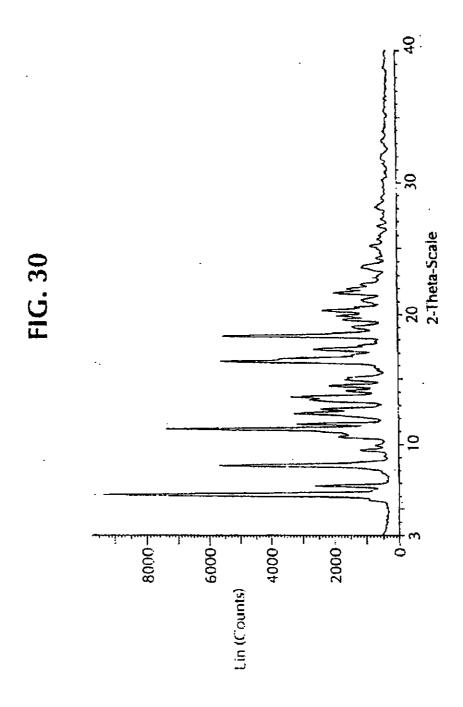


U.S. Patent



Sheet 30 of 33

US 6,977,243 B2

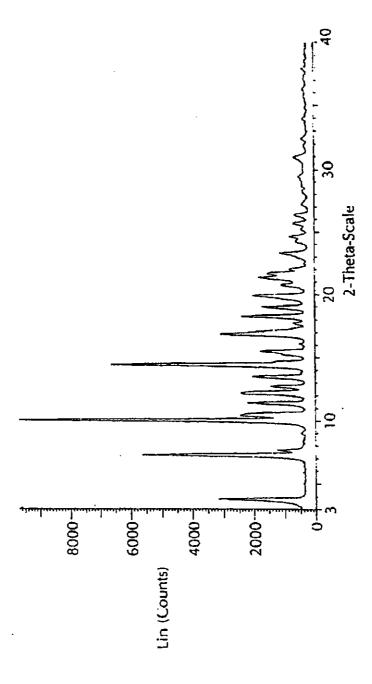


U.S. Patent

Dec. 20, 2005 Sheet 31 of 33

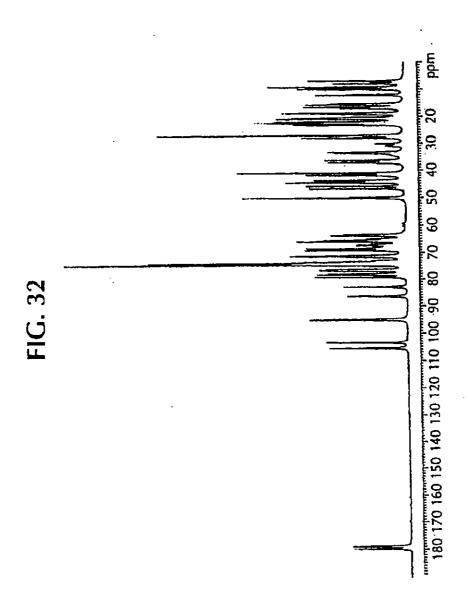
US 6,977,243 B2





Dec. 20, 2005

Sheet 32 of 33

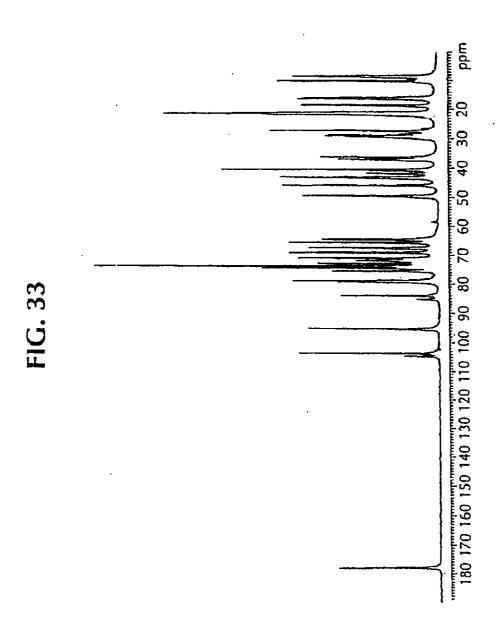


U.S. Patent

Dec. 20, 2005

Sheet 33 of 33

US 6,977,243 B2



1 CRYSTAL FORMS OF AZITHROMYCIN

This application claims the benefit of U.S. Provisional Application Ser. No. 60/292,565, filed May 22, 2001; U.S. Provisional Application Ser. No. 60/297,741, filed Jun. 12, 2001; and U.S. Provisional Application Ser. No. 60/343,041, filed Dec. 21, 2001, the contents of the aforementioned provisional patent applications are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

This invention relates to crystal forms of azithromycin. Azithromycin is sold commercially and is an effective antibiotic in the treatment of a broad range of bacterial infections. The crystal forms of this invention are likewise useful as antibiotic agents in mammals, including man, as well as in fish and birds.

Azithromycin has the following structural formula:

Azithromycin is described and claimed in U.S. Pat. Nos. 4,517,359 and 4,474,768. It is also known as 9-deoxo-9a-aza-9a-methyl-9a-homoerythomycin A.

Other patents or patent applications which directly or 40 indirectly cover azithromycin include: EP 298,650 which claims azithromycin dihydrate; U.S. Pat. No. 4,963,531 which claims a method of treating a strain of Toxoplasma gondii species; U.S. Pat. No. 5,633,006 which claims a chewable tablet or liquid suspension pharmaceutical com- 45 position having reduced bitterness; U.S. Pat. No. 5,686,587 which claims an intermediate useful in the preparation of azithromycin; U.S. Pat. No. 5,605,889 which claims an oral dosage form that reduces the "food effect" associated with the administration of azithromycin; U.S. Pat. No. 6,068,859 so which claims a controlled dosage form containing azithromycin; U.S. Pat. No. 5,498,699 which claims a composition containing azithromycin in combination with bivalent or trivalent metals; EP 925,789 which claims a method of treating eye infections; Chinese patent application CN 55 1123279A which relates to water soluble salts of azithromycin; Chinese patent application CN 1046945C which relates to azithromycin sodium dihydrogenphosphate double salts; Chinese patent application CN 1114960A which relates to azithromycin crystals, Chinese patent application 60 CN 1161971A which relates to azithromycin crystals; Chinese patent application CN 1205338A which relates to a method of preparing water soluble salts of azithromycin; International Publication WO 00/32203 which relates to an ethanolate of azithromycin; and European patent application 65 EP 984,020 which relates to an azithromycin monohydrate isopropanol clathrate.

SUMMARY OF THE INVENTION

The present invention relates to crystal forms of azithromycin. As used herein, the term "crystal form(s)" or "form(s)", unless otherwise noted, means one or more crystal forms of azithromycin.

In particular, the present invention relates to a crystal form of azithromycin wherein said crystal form is selected from forms C, D, E, F, G, H, J, M, N, O, P, Q and R wherein said forms are as defined herein. Forms F, G, H, J, M, N, O, and P belong to family I azithromycin and belong to a monochinic P2, space group with cell dimensions of a=16.3±0.3 Å, b=16.2±0.3 Å, c=18.4±0.3 Å and beta=109±2°. Forms C, D, E and R belong to family II azithromycin and belong to an orthorhombic P2, 2,2, space group with cell dimensions of a=8.9±0.4 Å, b=12.3±0.5 Å and c=45.8±0.5 Å. Form Q is distinct from families I and II.

Form F azithromycin is of the formula C₃₈H₇₂N₂O₁₂.H₂O.0.5C₂H₅OH in the single crystal structure, being azithromycin monohydrate hemi-ethanol solvate. Form F is further characterized as containing 2-5% water and 1-4% ethanol by weight in powder samples and having powder X-ray diffraction 28 peaks as defined in Table 9. The ¹³C saNMR (solid state Nuclear Magnetic 25 Resonance) spectrum of form F has two chemical shift peaks at approximately 179±1 ppm, those being 179.5±0.2 ppm and 178.6±0.2 ppm, a set of five peaks between 6.4 to 11.0 ppm, and ethanol peaks at 58.0±0.5 ppm and 17.2±0.5 ppm. The solvent peaks can be broad and relatively weak in 30 intensity.

The invention also relates to substantially pure form F azithromycin, form F azithromycin substantially free of form G azithromycin and form F azithromycin substantially free of azithromycin dihydrate.

The invention further relates to methods of preparing form F azithromycin by treating azithromycin with ethanol to complete dissolution at 40-70° C. and cooling with reduction of ethanol or addition of water to effect crystallization. Also included are methods of making substantially pure form F azithromycin, form F azithromycin substantially free of form G azithromycin and form F azithromycin substantially free of azithromycin dihydrate.

Form G azithromycin is of the formula $C_{28}H_{72}N_2O_{12}.1.5H_2O$ in the single crystal structure, being azithromycin sesquihydrate. Form G is further characterized as containing 2.5-6% water and <1% organic solvent(s) by weight in powder samples and having powder X-ray diffraction 29 peaks as defined in Table 9. The ¹³C saNMR spectrum of form G has one chemical shift peak at approximately 179±1 ppm, being a peak at 179.5±0.2 ppm (splitting <0.3 ppm may present), and a set of five peaks between 6.3 to 11.0 ppm.

The invention also relates to substantially pure form G azithromycin, and form G azithromycin substantially free of azithromycin dihydrate.

The invention further relates to methods of preparing substantially pure form G azithromycin, and form G azithromycin substantially free of azithromycin dibydrate by treating azithromycin with a mixture of methanol and water or acetone and water to complete dissolution at 40-60° C, and cooling to effect crystallization.

Form H azithromycin is of the formula $C_{2a}H_{12}N_{1}O_{12}H_{2}O.C_{3}H_{a}O_{2}$ being azithromycin monohydrate hemi-1,2 propanediol solvate.

Form I azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_3H_7OH$ in the single crystal

structure, being azithromycin monohydrate hemi-npropanol solvate. Form J is further characterized as containing 2-5% water and 1-5% 1-propanol by weight in powder samples and having powder X-ray diffraction 28 peaks as defined in Table 9. The ¹³C ssNMR spectrum of form J has 5 two chemical shift peaks at approximately 179:1: ppm, those being 179.6:20.2 ppm and 178.4:20.2 ppm, a set of five peaks between 6.6 to 11.7 ppm and an n-propanol peak at 25.2:20.4 ppm. The solvent peak can be broad and relatively weak in intensity.

The invention further relates to methods of preparing form J by treating azithromycin with n-propanol to complete dissolution at 25-55° C. and cooling with addition of water to effect crystallization.

Form M azithromycin is of the formula 15 C₃₈H₇₂N₂O₁₃.H₂O.0.5C₃H₇OH, being azithromycin monohydrate hemi-isopropanol solvate. Form M is further characterized as containing 2-5% water and 1-4% 2-propanol by weight in powder samples and having powder X-ray diffraction 26 peaks as defined in Table 9. The ¹³C ssNMR ²⁰ spectrum of form M has one chemical shift peak at approximately 179±1 ppm, being 179.6±0.2 ppm, a peak at 41.9±0.2 ppm and a set of six peaks between 6.9 to 16.4 ppm and an isopropanol peak at 26.0±0.4 ppm. The solvent peak can be broad and relatively weak in intensity.

The invention also relates to substantially pure form M azithromycin, form M azithromycin substantially free of form G azithromycin and form M azithromycin substantially free of azithromycin dihydrate.

The invention further relates to methods of preparing substantially pure form M azithromycin, form M azithromycin substantially free of form G azithromycin and form M azithromycin aubstantially free of azithromycin dihydrate by treating azithromycin with isopropanol to complete dissoution at 40-60° C. and reduction of isopropanol followed by cooling or cooling followed by addition of water to effect crystallization.

Form Nazithromycin is a mixture of isomorphs of Family I. The mixture may contain variable percentages of 40 isomorphs, R, G, H, J, M and others, and variable amounts of water and organic solvents, such as ethanol, isopropanol, appropanol, propylene glycol, acetone, acetonitrile, butanol, pentanol, etc. The weight percent of water can range from 1-5% and the total weight percent of organic solvents can be 45 2-5% with each solvent content of 0.5 to 4%. The samples of form N display all characteristic peaks of members of Family I in various proportions. Form N may be characterized as 'mixed crystals' or "crystalline solid solutions' of Family I isomorphs.

Form N displays chemical shifts as a combination of isomorphs in Family I. The peaks may vary in chemical shift ppm within ±0.2 ppm and in relative intensities and width due to the mixing of variable proportion of isomorphs contained in the form N crystalline solid solution.

Form P azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_2H_{12}O$ being azithromycin monohydrate hemi-n-pentanol solvate.

Form Q azithromycin is of the formula $C_{3a}H_{72}N_2O_{12}.H_2O.0.5C_aH_8O$ being azithromycin monohydrate hemi-tetrahydrofuran solvate.

Form R azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.C_3H_{12}O$ being azithromycin monohydrate mono-methyl tert-butyl ether solvate.

Porm D azithromycin is of the formula $C_{34}H_{72}N_2O_{12}.H_2O.C_6H_{12}$ in its single crystal structure,

being azithromycin monohydrate monocyclohexane solvate. Form D is further characterized as containing 2-6% water and 3-12% cyclohexane by weight in powder samples and having representative powder X-ray diffraction 20 peaks as defined in Table 9. The ¹³C ssNMR spectrum of form D displays has one chemical shift peak at approximately 179±1 ppm, being 178.1±0.2 ppm and peaks at 103.9±0.2ppm, 95.1±0.2 ppm, 84.2±0.2 ppm, and a set of 3 peaks between 8.4 to 11 ppm.

The invention further relates to methods of preparing form D by sturrying azithromycin dihydrate with cyclohexane.

Form E szithromycin is of the formula $C_{36}H_{72}N_2O_{12}.H_2O.C_4H_6O$ being szithromycin monohydrate mono-tetrahydrofuran solvate.

The invention further relates to azithromycin in an amorphous state and a method of preparing amorphous azithromycin that comprises the removal of water and/or solvents from the azithromycin crystal lattice. The X-ray diffraction powder pattern for amorphous azithromycin displays no sharp 20 peaks but has two broad rounded peaks. The first peak occurs between 4° and 13°. The second peak occurs between 13° and 25°.

The invention also relates to pharmaceutical compositions for the treatment of a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises a therapeutically effective amount of the crystalline compounds referred to above, or amorphous azithromycin, and a pharmaceutically acceptable carrier.

The invention also relates to a method of treating a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of the crystalline compounds referred to above, or amorphous azithromycin.

The present invention also relates to methods of preparing crystal forms of azithromycin which comprise the slurying of azithromycin in an appropriate solvent or the dissolution of azithromycin in a heated organic solvent or organic solvent/water solution and precipitating the crystalline azithromycin by cooling the solution with reduction of solvent volume or by dissolving azithromycin in a solvent or solvent mixture and precipitating crystalline azithromycin by the addition of water to the solution. Azithromycin in amorphous state is prepared by heating crystalline azithromycin in a vacuum.

The term "reatment", as used herein, unless otherwise indicated, means the treatment or prevention of a bacterial infection or protozoa infection as provided in the method of the present invention, including curing, reducing the symptoms of or slowing the progress of said infection. The terms "treat" and "treating" are defined in accord the foregoing term "treatment".

The term "substantially free" when referring to a designated crystalline form of azithromycin means that there is less than 20% (by weight) of the designated crystalline form(s) present, more preferably, there is less than 10% (by weight) of the designated form(s) present, more preferably, there is less than 10% (by the is less than 5% (by weight) of the designated form(s) present, and most preferably, there is less than 1% (by weight) of the designated crystalline form(s) present. For instance, form F azithromycin substantially free of azithromycin dihydrate means form F with 20% (by weight) or less of azithromycin dihydrate, more preferably, 10% (by weight) or less of azithromycin dihydrate, most preferably, 15% (by weight) of azithromycin dihydrate.

The term "substantially pure" when referring to a designated crystalline form of azithromycin means that the des-

ignated crystalline form contains less than 20% (by weight) of reaidual components such as alternate polymorphic or isomorphic crystalline form(s) of azithromycin. It is preferred that a substantially pure form of azithromycin contain less than 10% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin, more preferred is less than 5% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin, and most preferably less than 1% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin.

The term "substantially in the absence of azithromycin dihydrate" when referring to bulk crystalline azithromycin or a composition containing crystalline azithromycin means the crystalline azithromycin contains less than about 5% (by weight) azithromycin dihydrate, more preferably less than 15 about 3% (by weight) azithromycin dihydrate, and most preferably less than 1% (by weight) azithromycin dihydrate.

As used herein, unless otherwise indicated, the term "bacterial infection(s)" or "protozoa infection" includes bacterial infections and protozoa infections and diseases 20 caused by such infections that occur in mammals, fish and birds as well as disorders related to bacterial infections and protozoa infections that may be treated or prevented by administering antibiotics such as the compound of the present invention. Such bacterial infections and protozoa 25 infections and disorders related to such infectious include, but are not limited to, the following: pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, and mastoiditis related to infection by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus 30 aureus, or Peptostreptococcus spp.; pharynigitis, rheumatic fever, and glomerulonephritis related to infection by Streptococcus pyogenes, Groups C and G streptococci, Clostridium diptheriae, or Actinobacillus haemolyticum; respiratory tract infections related to infection by Myco- 35 plasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae, or Chlamydia pneumoniae; uncomplicated skin and soft tissus infections, abscesses and osteomyelitis, and puerperal fever related to infection by Staphylococcus aureus, conquiese-positive sta- 40 phylococci (i.e., S. epidermidis, S. hemolyticus, etc.), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, Carynebacterium minutissimum, Clastridium spp., or Bartonella henselae; uncomplicated acute urinary 45 tract infections related to infection by Staphylococcus saprophyticus of Enterococcus spp.; urethritis and cervicitis; and sexually transmitted diseases related to infection by Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum, ot Neiserria gonor- 50 rheae; toxin diseases related to infection by S. aureus (food poisoning and Toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by Helicobacter pylori; systemic febrile syndromes related to infection by Borrella recurrentis, Lyme disease related to infection by 55 Borrelia burgdorferi; conjunctivitis, keratitis, and dacrocystitis related to infection by Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae, or Listeria spp.; disseminated Mycobacterium avium complex (MAC) disease related to infection by Mycobacterium avium, or Mycobacterium intracellulare; gastroenteritis related to infection by Campylobacter jejuni; intestinal protozoa related to infection by Cryptosportdium spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by Bordetella 65 pertussis, gas gangrene related to infection by Clostridium perfringens or Bacteroldes spp.; and atherosclerosis related

6

to infection by Helicobacter pylori or Chlamydia pneumoniae. Also included are atherosclerosis and malaria. Bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in animals include, but are not limited to, the following: bovine respiratory disease related to infection by P. haem., P. multocida, Mycoplasma bovis, or Bordetella spp.; cow enteric disease related to infection by E. coli or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella spp., Carynebacterium, or Enterococcus spp.; swine respiratory disease related to infection by A. pleuro., P. multocida, or Mycoplasma spp.; swine enteric disease related to infection by E. coll, Lawsonia intracellularis, Salmonella, or Serpulina hyodylsinteriae: cow footrot related to infection by Fusobacterium spp.; cow metritis related to infection by E. coll; cow hairy warts related to infection by Fusobacterium necrophorum or Bacteroides nodosus; cow pink-eye related to infection by Moraxella bovis; cow premature abortion related to infection by protozoa (i.e. neceporium); urinary tract infection in dogs and cats related to infection by E. coll. skin and soft tissue infections in dogs and cats related to infection by Staph. epidermidis, Staph. intermedius, coagulase neg. Staph. or P. multocida; and dental or mouth infections in dogs and cats related to infection by Alcaligenes spp., Bacteroldes spp., Clastridium spp., Enterobacter spp., Eubacterium, Peptostreptococcus, Porphyromonas, or Prevotella. Other bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

The present invention also includes isotopically-labeled compounds wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, caygen, phosphorous, sulfur, fluorine and chlorine, such as ²H, ³H, ³C, ¹⁴C, ¹⁵N, ¹⁸O, and ³⁷O. Such radiolabelled and stable-isotopically labelled compounds are useful as research or diagnostic tools.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a calculated powder X-ray diffraction pattern of azithromycin form A. The scale of the abscissa is degrees 2-theta (2 8). The ordinate is the intensity in counts.

FIG. 2 is an experimental powder X-ray diffraction pattern of azithromycin form A. The scale of the abscissa is in degrees 2-theta (20). The ordinate is the intensity in counts.

FIG. 3 is an overlay of FIGS. 1 and 2 with the calculated diffraction patterns of azithromycin form A (FIG. 1) on the bottom and the experimental diffraction pattern of azithromycin form A (FIG. 2) on the top. The scale of the abscissa is in degrees 2-theta (2 8). The ordinate is the intensity in counts.

FIG. 4 is a calculated powder X-ray diffraction pattern of azithromycin form C. The scale of the abscissa is in degrees 2-theta (2 0). The ordinate is the intensity in counts.

FIG. 5 is a calculated powder X-ray diffraction pattern of azithromycin form D. The scale of the abscissa is in degrees 2-theta $(2 \ \theta)$. The ordinate is the intensity in counts.

FIG. 6 is an experimental powder X-ray diffraction pattern of azithromycin form D. The scale of the abscissa is in degrees 2-theta (20). The ordinate is the intensity in counts.

FIG. 7 is an overlay of FIGS. 5 and 6 with the calculated diffraction pattern of azithromycin form D (FIG. 5) on the bottom and the experimental diffraction pattern of azithromycin form D (FIG. 6) on the top. The scale of the abscissa is in degrees 2-theta (2 0). The ordinate is the intensity in s mycin form G.

FIG. 8 is a calculated powder X-ray diffraction pattern of azithromycin form E. The scale of the abacissa is in degrees 2-theta (2 0). The ordinate is the intensity in counts.

FIG. 9 is a calculated powder X-ray diffraction pattern of 10 azithromycin form F. The scale of the abscissa is in degrees 2-theta (2 β). The ordinate is the intensity in counts.

FIG. 10 is an experimental powder X-ray diffraction pattern of azithromycin form P. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in

FIG. 11 is an overlay of PIGS. 9 and 10 with the calculated diffraction pattern of azithromycin form F (FIG. 9) on the bottom and the experimental diffraction pattern of 20 azithromycin form F (FIG. 10) on the top. The scale of the abacissa is in degrees 2-theta (2 8). The ordinate is the

FIG. 12 is a calculated powder X-ray diffraction pattern of azithromycin form G. The scale of the abscissa is in degrees 25 2-theta (2 θ). The ordinate is the intensity is counts.

FIG. 13 is an experimental powder X-ray diffraction pattern of azithromycin form G. The scale of the abscissa is in degrees 2-theta (2 8). The ordinate is the intensity in COUNTS.

FIG. 14 is an overlay of FIGS. 12 and 13 with the calculated diffraction pattern of azithromycin form G (FIG. 12) on the bottom and the experimental diffraction pattern of azithromycin form G (FIG. 13) on the top. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the 35 intensity in counts.

FIG. 15 is a calculated powder X-ray diffraction pattern of azifhromycin form J. The scale of the abscissa is in degrees 2-theta ($\bar{2}$ θ). The ordinate is the intensity in counts.

FIG. 16 is an experimental powder X-ray diffraction pattern of azithromycin form J. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in comis.

FIG. 17 is an overlay of FIGS. 15 and 16 with the 45 calculated diffraction pattern of azithromycin form J (FIG. 15) on the bottom and the experimental diffraction pattern of azithromycin form I (FIG. 16) on the top. The scale of the abscissa is in degrees 2-theta (2 0). The ordinate is the intensity in counts.

FIG. 18 is an experimental powder X-ray diffraction pattern of azithromycin form M. The scale of the abscissa is in degrees 2-theta (2 0). The ordinate is the intensity in

FIG. 19 is an experimental powder X-ray diffraction 55 pattern of azithromycin form N. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in

FIG. 20 is an experimental powder X-ray diffraction 60 pattern of amorphous azithromycin. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 21 is a ¹³C solid state NMR spectrum of azithromycin form A.

FIG. 22 is a ¹³C solid state NMR spectrum of azithro-

8

FIG. 23 is a ¹³C solid state NMR spectrum of azithromycin form F.

FIG. 24 is a ¹³C solid state NMR spectrum of azithro-

FIG. 25 is a ¹³C solid state NMR spectrum of azithromycin form J.

FIG. 26 is a ¹³C solid state NMR spectrum of azithromycin form M.

FIG. 27 is a ¹³C solid state NMR spectrum of azithmmycin form N.

FIG. 28 is a ¹⁹C solid state NMR spectrum of amorphous azithromycin.

FIG. 29 is a ¹³C solid state NMR spectrum of a pharmacentical tablet containing form G azithromycin.

PIG. 30 is an experimental powder X-ray diffraction pattern of azithromycin form Q. The scale of the abscissa is in degrees 2-theta (2 0). The ordinate is the intensity in

FIG. 31 is an experimental powder X-ray diffraction pattern of azithromycin form R. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in

FIG. 32 is a 13 C solid state NMR spectrum of azithromycin form H.

FIG. 33 is a ¹³C solid state NMR spectrum of azithromycin form R.

DETAILED DESCRIPTION OF THE INVENTION

Azithromycin has been found to exist in different crystalline forms. A dihydrate, form A, and a non-stroichiometric hydrate, form B, are disclosed in European Patent EP 298 650 and U.S. Pat. No. 4,512,359, respectively. Sixteen other forms have been discovered, namely forms C, D, E, F, G, H, 1, J, K, L, M, N, O, P, Q and R. These forms are either hydrates or hydrate/solvates of azithromycin free base. Forms L and K are the metastable lower hydrate forms of A, detected at high temperature. Crystal structures of forms A. C, D, E, F, G, H, J and O have been solved. The structural data of these crystal forms are given below:

TABLE 1

Crystallographic dat	a of estitivomycia form 🛦
	Form A
Empirical formula Formula weight Cystel size (mm) Space group Unit cell dimensions	C ₂₀ H ₇₂ N ₂ O ₁₂ 2H ₂ O 783.2 0.19 × 0.24 × 0.36 F1,2/2, orthorhombic a ~ 14.735 (5) Å b = 16.844 (7) Å c = 17.81 (1) Å a = 90° 6 = 90°
Z (per formula) Density (g/cm²) R	7 = 90° 4 1.18 0.060

10

TA	BLE 2		TABI	E 5-continued
Crystallographic data	of midmomycia form C.		Crystallographic	data of azithromycla form R
	Forms C	5		Form F
Empirical formula Formula weight Crystal size (mm) Space group Unit cell dimensions	C ₂₆ H ₇₂ N ₂ O ₁₂ ·H ₂ O 767.15 0.16 × 0.16 × 0.19 F2 ₁ 2 ₁ 2 ₁ orthorhombic a = 8.809 (3) Å b = 12.4750 (8) Å c = 45.59 (3) Å	10	Z (per formula) Density (g/cm²) R	α = 90° β = 109.33(1)° γ = 90° 4 1.13 0.0688
	α = 90° β = 90° γ = 90°	15		MATNETI C
Z (per formula) Density (g/cm²)	4 1.01	- ¹³ —		TABLE 6
R	0.106		Change	data of arithmenyois form G. Form G
	BLE 3	20 -	Formula Formula weight Crystal size (mm) Space group	C ₂₆ H ₇₂ N ₂ O ₁₂ J.5H ₂ O 776.0 0.04 × 0.20 × 0.24 P2 ₁ monoclinic
24 Anni Antonia mercani	Porm. D		Unit cell dimensions	e = 16.4069(8) Å b = 16.2972(8) Å c = 18.3830 (9) Å
Empirical formula Pormula weight Crystal size (mm) Space group Unit cell dimensions	C ₃₂ H ₂₂ N ₂ O ₃₂ H ₂ O,C ₆ H ₁₂ 851.15 0.52 × 0.32 × 0.16 P2,2,2, orthothomble s = 8.8710 (10) Å b = 12.506 (2) Å	25	Z (per formula) Desaity (g/cm²) R	α = 90° β = 110.212(2)" γ = 90° 4 1.12 0.0785
Z (per formula) Density (g/cm²)	c = 45.697 (7) Å α = 90° β = 90° γ = 90° 4 1.12	30 35 ·	Crystallographic	TABLE 7
R	0,0663			Form El
	ABLE 4	_ 	Empirical formula Crystal size (mm) Formula weight Space group Unit cell dimensions	C ₂₆ H ₂₇ N ₂ O ₁₂ H ₂ O _{.0.5} C ₂ H ₂ O ₂ 0.14 × 0.20 × 0.24 805.0 P2, monoclinic a = 16.177 (1) Å
	Form E			b = 16.741 (2) Å c = 18.614 (1) Å
Empirical formula Formula weight Crystal size (cum) Space group Unit cell dimensions	C ₂₄ H ₇₂ N ₂ O ₁₂ H ₂ O,C ₄ H ₆ O 839.2 0.17 × 0.19 × 0.20 P2,2,2, orborhombic a = 8.869 (3) Å b = 12.066 (3) Å	45	Z (per formula) Density (g/cm²) R	α = 90" β = 108.34 (1)" γ = 90" 4 . 1.15 0.0687
Z (per formula)	c = 46.00 (1) Å α = 90° β = 90° γ = 90° 4	50		TABLE 8
Density (g/cm³) R	1.13 0.087		Crystallographi	c deta of azithromycin form J.
		55	Portuula Fortuula welght	Form J C ₂₆ H ₇₂ N ₂ O ₁₂ H ₂ O.0.5C ₂ H ₆ O 796.0
	ABLE 5		Crystal size (mm) Space group	0.40 × 0.36 × 0.20 P2, monoclinic
Crystaliographic d	ta of exithromycin form R. Form P	60	Unit cell dimensions	s = 16,191(6) Å b = 16,237(10) Å c = 18,595(14) Å
Empirical formula Crystal time (mm) Formula weight Spare group Unit cell dimensions	C ₂₈ H ₁₂ N ₂ O ₁₂ H ₂ O.0.5C ₂ H ₄ O 0.14 x 0.20 x 0.24 790.2 P2 ₁ monoclinic a = 16.281 (2) Å b = 16.293(1) Å c = 18.490 (3) Å	65 	Z (per formula) Density (g/cm²) R	α = 90° β = 108.92(4)° γ = 90° 4 1.14 0.0789

11

TABLE 8A

Crystallogypobie	c dain of grithromyciz form O.
	Form O
Formula Formula weight Crystal size (mm) Space george Unit cell dimensions	$C_{20}H_{22}N_2O_{12}O.5H_2O.0.5C_4H_{42}O$ 795.04 0.40 × 0.36 × 0.20 P2, mosoclinic $n = 16.3692(11)$ Å $b = 16.2042(11)$ Å $c = 18.5459(12)$ Å $a = 90^{\circ}$ $\beta = 109.66(10)^{\circ}$
Z (per formula) Density (g/cm²) R	7 = 90° 4 1.14 0.0421

Among these sixteen crystal forms, two isomorphic families are identified. Family I includes forms F, G, H, J, M, N, 20 O, and P. Family II includes forms C, D, E and R. Form Q is distinct from families I and II. The forms within a family are isomorphs that crystallize in the same space group with slight variation of cell parameters and comprise chemically related structures but different elemental composition. In this case, the variation in chemical composition among the isomorphs arises from incorporation of different water/ solvent molecules. Consequently, the isomorphs display similar but non-identical X-ray diffraction patterns and solid-state NMR spectra (anNMR). Other techniques such as near infrared spectroscopy (NIR), differential scanning calo. 30 rimetry (DSC), gas chromatography (GC), thermalgravimetric analysis (TGA), or thermalgravimetric analysis/infrared spectroscopy analysis (TG-IR), Karl Fischer water analysis (KF) and molecular modeling/visualization provide data for affirmative identification of isomorphs. Dehydration/ 35 1% of the corresponding solvent used for crystallization, desolvation temperatures were determined by DSC with a heating rate of 5° C/min Form C

This crystal form was identified from a single crystal structure (Table 2)—a monohydrate of azithromycin. It has 40 the space group of P2,2,2,, and similar cell parameters as that of forms D and E; therefore, it belongs to Family II isomorphs. Its calculated powder pattern is similar to that of forms D and E. Form D

Form D was crystallized from cyclohexans. The single crystal structure of form D shows a stoichiometry of a monohydrate/monocyclohexane solvate of azithromycin (Table 3). Cyclohexane molecules were found to be disordered in the crystal lattice. From single crystal data, the 50 calculated water and cyclohexane content of form D is 2.1 and 9.9%, respectively. Both the powder pattern and the calculated powder pattern of form D are similar to those of forms C and E. The powder samples of form D showed a desolvation/dehydration endotherm with an onset tempera- 55 ture of about 87° C. and a broad endotherm between 200-280° C. (decomposition) in DSC analysis at 5°C./min from 30-300° C.

Form D is prepared by slurrying azithromycin in cyclohexane for 2-4 days. The solid form D azithromycin is 60 collected by filtration and dried. Form E

Form E was obtained as a single crystal collected in a THF/water medium, it is a monohydrate and mono-THF solvate by single crystal analysis (Table 4). By its single 65 crystal structure, the calculated PXRD pattern is similar to that of form C and form D making it a family II isomorph.

12

Form E is prepared by dissolving azithromycin in THF (tetrahydrofuran). Diffusing water vapor through saturated azithromycin THF solution over time yields crystals of Form

5 Form F

The single crystal of form F crystallized in a monoclinic space group, P21, with the asymmetric unit containing two azithromycin, two waters, and one ethanol, as a monohydrate/hemi-ethanolate (Table 5). It is isomorphic to all family I azithromycin crystalline forms. The calculated PXRD pattern of this form is similar to those of other family I isomorphs. The theoretical water and ethanol contents are 2.3 and 2.9%, respectively. The powder samples show a dehydration/desolvation endotherm at an onset temperature between 110-125° C. Form F is prepared by dissolving azithromycin in ethanol (1-3 volumes by weight) at a temperature of about 50-70° C. Upon complete dissolution, the solution is cooled to subambient temperature to cause precipitation. The volume of ethanol can be reduced by vacuum distillation with stirring for 1-2 hours to increase the yield. Alternatively, water (optionally chilled to 0-20° C.) about 0.1-2 volume can be added with collection of solids within 30 minute after water addition. Cooling the ethanol solution of azithromycin prior to the addition of water to below below 20° C., preferably below 15° C., more preferably below 10, and most preferably 5° C. results in substantially pure azithromycin form F. The solid form P azithromycin is collected by filtration and dried.

The single crystal structure of form G consists of two azithromycin molecules and three water molecules per asymmetric unit (Table 6). This corresponds to a sesquibydrate with a theoretical water content of 3.5%. The water content of powder samples of form G ranges from about 2.5 to about 6%. The total residual organic solvent is less than which is well below stoichiometric quantities of solvate. This form dehydrates with an onset temperature of about 110-120° C.

Form G may be prepared by adding azithromycin to a premixed organic solvent/water mixture (1/1 by volume), where the organic solvent can be methanol, acctone, accionitrile, ethanol or isopropanol. The mixture is stirred and heated to an elevated temperature, e.g. 45-55° C. for 4-6 hours to cause dissolution. Precipitation occurs during cooling to ambient temperature. The solid form G azithromycin is collected by filtration and dried. Form H

This crystal form is a monohydrate/hemi-propylene glycol solvate of azithromycin free base (Table 7). It was isolated from a formulation solution containing propylene glycol. The crystal structure of form H is isomorphic to crystal forms of Family I.

Azithromycin form H is prepared by dissolving azithromycin dihydrate in 6 volumes of propylene glycol. To the resulting propylene glycol solution of azithromycin, 2 volumes of water is added and precipitation occurs. The slurry is stirred for 24 hours and the solids are filtered and air-dried at ambient temperature to afford crystalline Form H. Form J

Form J is a monohydrate/hemi n-propanol solvate (Table 8). The calculated solvent content is about 3.8% n-propanol and about 2.3% water. The experimental data shows from about 2.5 to about 4.0% n-propanol and from about 2.5 to about 3% water content for powder samples. Its PXRD pattern is very similar to those of its isomorphs F, G, H, M and N. Like F and G, the powder samples have a dehydration/desolvation endotherm at 115-125° C.

Porm J is prepared by dissolving azithromycin in 4 volumes of n-propanol at a temperature of about 25-55° C. Water, about 6-7 volumes, is added at room temperature and the siurry is continuously stirred for 0.5-2 hours. The solid form J azithromycin is collected by filtration and dried. Form K

The PXRD pattern of form K was found in a mixture of azithromycin form A and microcrystalline wax after anneal ing at 95° C. for 3 hours. It is a lower hydrate of form A and is a metastable high temperature form. Form L

This form has only been observed upon heating the dihydrate; form A. In variable temperature powder X-ray diffraction (VT-PXRD) experiments, a new powder X-ray diffraction pattern appears when form A is heated to about 90° C. The new form, designated form L, is a lower hydrate 15 of form A because form A loses about 2.5 weight % at 90° C. by TGA, thus corresponding to a conversion to a monohydrate. When cooled to ambient temperature, form L rapidly reverts to form A. Form M

Isolated from an isopropanol/water slurry, form M incorporates both water and isopropanol. Its PXRD pattern and as-NMR spectrum are very similar to those of Family I isomorphs, indicating that it belongs to Family I. By analogy to the known crystal structures of Family I isomorphs, the 25 single crystal structure of form M would be a monohydrate/ hemi-isopropranolate. The dehydration/desolvation temperature of form M is about 115-125° C.

Form M may be prepared by dissolving azithromycin in 2-3 volumes of isopropanol (IPA) at 40-50° C. The solution 30 is cooled to below 15° C., preferably below 10° C., more preferably about 5° C, and 2-4 volumes of cold water about 5° C. are added to effect precipitation. Seeds of form M crystals may be added at the onset of crystallization. The shurry is stirred less than about 5 hours, preferably less than 35 about 3 hours, more preferably less than about 1 hour and most preferably about 30 minutes or less and the solids are collected by filtration. The solids may be resturried in isopropanol. This procedure provides form M substantially in the absence of azithromycin dihydrate. Form N

Isolated from water/ethanol/isopropanol shury of form A form N crystals may contain variable amounts of the crystallization solvents and water. Its water content varies from about 3.4 to about 5.3 weight percent. Analysis by GC Headspace reveals a variable solvent content of ethanol and isopropanol. The total solvent content of form N samples is usually lower than about 5% depending on the conditions of preparation and drying. The PXRD pattern of form N is similar to that of forms F, G, H, J and M of the Family I so isomorphs. The dehydration/desolvation endotherm(s) of the samples of form N may be broader and may vary between 110-130° C

Form N azithromycin may be prepared by recrystallizing azithromycin from a mixture of azithromycin crystal latice- 55 incorporating organic solvents and water, such as ethanol, isopropanol, n-propanol, acetone, acetomitrile etc. The solvent mixture is heated to 45-60° C. and azithromycin is added to the heated solvent mixture, up to a total of about 4 volumes. Upon dissolution, 1-3 volumes of water are added 60 with continuous agitation at 45-60° C. Form N azithromycin precipitates as a white solid. The slurry is allowed to cool to ambient temperature with stirring. Solid form N azithromycin is isolated by filtration and dried. Form O

This crystal form is a hemihydrate hemi-n-butanol solvate of azithromycin free base by single crystal structural data

14

(Table 8A). It was isolated from n-butanol solution of azithromycin with diffusion of antisolvent. The crystal struc-

here of form O is isomorphic to crystal forms of Family I.

Azithromycin is completely dissolved in n-butanol. Addition of an antisolvent, such as hexane, water, IPE or other non-solvent, by diffusion results in precipitation of Form O.

This is a proposed crystal form, being a hemihydrate hemi-n-pentanol solvate of azithromycin free base. It can be isolated from an n-pentanol solution of azithromyoin with diffusion of an antisolvent. The crystal structure of form P is isomorphic to crystal forms of Family I.

Form P of azithromycin may be prepared as following: Azithromycin is completely dissolved in n-pentanol; addition of an antisolvent, such as hexane, water, isopropyl other (IPE) or other non-solvent, by diffusion results in precipitation of Form P. Form O

The crystal form of Q exhibits a unique powder X-ray diffraction pattern. It contains about 4% water and about 4.5% THF, being a hydrate hemi THF solvate. The main dehydration/desolvation temperature is from about 80 to about 110° C.

Azithromycia dibydrate is dissolved in 6 volumes of THF and 2 volumes of water are added. The solution is allowed to evaporate to dryness at ambient conditions to afford crystalline Form O. Form R

This crystalline form is prepared by adding amorphous azithromycin to 2.5 volumes of tert-butyl methyl ether (MTBE). The resulting thick white suspension is stirred 3 days at ambient conditions. Solids are collected by vacuum filtration and air dried. The resulting bulk azithromycin form R has a theoretical water content of 2.1 weight % and a theoretical methyl tert-butyl ether content of 10.3 weight %.

Due to the similarity in their structures, isomorphs have proposity to form a mixture of the forms within a family, sometimes termed as 'mixed crystals' or 'crystalline solid solution'. Form N is such a solid crystalline solution and was found to be a mixture of Family I isomorphs by solvent composition and solid-state NMR data.

Both Pamily I and Family II isomorphs are hydrates and/or solvates of azithromycin. The solvent molecules in the cavities have tendency to exchange between solvent and water under specific conditions. Therefore, the solvent/water content of the isomorphs may vary to a certain extent.

The crystal forms of isomorphic Family I are more stable than form A when subjected to heating. Forms F, G, H, J, M and N showed higher onset debydration temperatures at 110-125° C. 110-125° C, than that of form A with an onset dehydration temperature at about 90 to about 110° C. and simultaneous solid-state conversion to form L at about 90°

Amorphous Azithromycin

All crystal forms of azithromycin contain water or solvent(s) or both water and solvent(s). When water and solvent(s) are removed from the crystalline solids, azithromyciu becomes amorphous. Amorphous solids have advantages of high initial dissolution rates.

The starting material for the synthesis of the various crystal forms in the examples below was azithromycin dihydrate unless otherwise noted. Other forms of azithmmycin such as amosphous azithromycin or other nondihydrate crystalline forms of azithromycin may be used.

EXAMPLES.

Example 1

Preparation of Form D

Form D was prepared by slurrying azithromycin dihydrate in cyclobexane for 2-4 days at an elevated temperature, e.g.

25-50° C. The crystalline solids of form D were collected by filtration and dried.

Example 2

Preparation of Form F

Azithromycin dihydrate was slowly added to one volume of warm othanol, about 70° C., and stirred to complete dissolution at 65 to 70° C. The solution was allowed to cool gradually to 2-5° C, and one volume of chilied water was added. The crystalline solids were collected shortly (proferably less than 30 minutes) after addition of water by vacuum filtration.

2R:

Azithromycin dihydrate is slowly added to one volume of warm ethanol, about 70° C., and stirred to complete dissolution at 65 to 70° C. The solution is allowed to cool gradually to 2-5° C. and ethanol volume may be reduced by vacuum distillation. Seeds of Form F 1-2% wt may be introduced to facilitate the crystallization. After stirring up to 2 hours the crystalline solids are collected by vacuum filtration. The isolation of the crystals yields substantially nure form F azithromycin, form F azithromycin substantially free of form G azithromycin and form F azithromycin 25 substantially free of azithromycin dihydrate.

Example 3

Preparation of Form G

A reaction vessel was charged with form A azithromycia. In a separate vessel, 1.5 volumes methanol and 1.5 volumes water were mixed. The solvent mixture was added to the reaction vessel containing the form A azithromycin. The shurry was stirred with heating to 50° C. for approximately 35 5 hours. Heating was discontinued and the slurry was allowed to cool with stirring to ambient temperature. The form G azithromycin was collected by filtration and allowed to air dry for approximately 30 minutes. The collected form G azithromycin was further dried in a vacuum oven at 45° C. This procedure yields substantially pure form G azithromycin, and form G azithromycin substantially free of azithromycin dihydrate.

Example 4

Preparation of Form J

Form I was prepared by dissolving azithromycin in 4 volumes of n-propanol at a temperature of about 25° C. Water (6.7 volumes) was added and the shury is continu- 50 ously stirred for 1 hour, followed by cooling to about 0° C. The solid form I azithromycin was collected by filtration and dried.

Example 5

Preparation of Form M Substantially in the Absence of Azithromycin Dihydrate

Azithromycin dihydrate is completely dissolved in 2 60 volumes of warm isopropanol 40-50° C. Seeds of Form M may be optionally introduced to facilitate the crystallization. The solution is then cooled to 0-5° C. and 4 volumes of chilled water as antisolvent are added and the solids are collected by vacuum filtration. The solids are resturted in 1 65 volume of isopropanol for 3-5 hours at 40-45° C. and then cooled to 0-5° C. The crystalline solids are collected shortly

(about 15 minutes) after addition of water by vacuum filtration. The solids are reshurried in 0.5 to 1 volume of isopropanol at 25-40° C. and cooled to about 5° C. followed by filtration to collect solids of form M.

These procedures yield substantially pure form M azithromycin, form M azithromycin substantially free of form G azithromycin and form M azithromycin substantially free of azithromycin dihydrate

Example 6

Preparation of Form N

Two volumes of ethanol and 2 volumes of isopropanol were added to a reaction vessel and heated to 50° C. 15 Azithromycin form A was added with stirring to the heated ethanol/isopropanol mixture to yield a clear solution. The reaction vessel was charged with 2 volumes distilled water (ambient temperature). Stirring was continued at 50° C, and solid form N azithromycin precipitated after approximately 1 hr. Heating was discontinued 5 hours after the addition of the water. The shurry was allowed to cool to ambient temperature. Precipitated form N azithromycin was collected by filtration and dried for 4 hours in vacuum oven at 45° C.

Example 7

Preparation of Amorphous Azithromycin

Crystalline form A azithromycin was heated to 110-120° 30 C. in an oven for overnight under vacuum. The amorphous solids were collected and stored with desiccant as needed.

Example 8

Preparation of Form H

Azithromycin dihydrate or other crystal forms was dissolved in 6 volumes of propylene glycol. To the resulting propylene glycol solution of azithromycin, 2 volumes of water were added and precipitation occurred. The sharry was 40 stirred for 24 hours and the solids were filtered and air-dried at ambient temperature to afford crystalline Form H.

Example 9

Preparation of Form Q

The crystalline powder was prepared by dissolving 500 mg azithromycin Form A in 2 ml THF. To the clear, coloneas solution at room temperature was added 1 ml water. When the solution became cloudy an additional 1 ml THF was added to dissolve the azithromycin completely, and the solution was stirred at ambient temperature. Solvent was allowed to evaporate over 7 days, after which the dry solids were collected and characterized.

Example 10

Powder X-ray Diffraction Analysis

55

Powder patterns were collected using a Bruker D5000 diffractometer (Madison, Wis.) equipped with copper radiation, fixed slits (1.0, 1.0, 0.6 mm), and a Kevex solid state detector. Data was collected from 3.0 to 40.0 degrees in 2 theta using a step size of 0.04 degrees and a step time of 1.0 seconds. The results are summarized in Table 9.

The experimental PXRD diffraction pattern of azithromycin form A is given in FIG. 2.

The experimental PXRD diffraction pattern of azithromycin form D is given in FIG. 6.

45

The experimental PXRD diffraction pattern of azithromycin form F is given in FIG. 10.

The experimental PXRD diffraction pattern of azithromycia form G is given in FIG. 13.

The experimental PXRD diffraction pattern of azithromy- 5 cin form J is given in FIG. 16.

The experimental PXRD diffraction pattern of azithromycin form M is given in FIG. 18.

The experimental PXRD diffraction pattern of azithromycin form N is given in FIG. 19.

The experimental PXRD diffraction pattern of amorphous azithromycin is given in FIG. 20.

The experimental PXRD diffraction pattern of azithromycin form Q is given in FIG. 30.

The experimental PXRD diffraction pattern of azithromycin form R is given in FIG. 31.

The experimental variability from sample to sample is about ±0.2° in 2 theta, and the same variations were observed between the calculated powder from single crystal 20 structure and experimental data. Detailed analysis showed that the isomorphs in Family I can be discerned by PXRD with sets of characteristic peaks given in Table 9.

TABLE 9

•							
	ripon.	vels Pow	er X-ray	Diffraction	Peaks in	2-tbeta z	0.2*
	D	F	G	7	M	N	Q
7.2	3.9	5.7	5.0	5.0	5.0	-62	5.7
7.9	7.3	_6.2	5.8	5,7	5.6	7.3	6.1
-2.3	7.7	7.4	62	_62	6.2	7.8	6.8
. 9.9	16.1	7.8	7.4	7.3	7.3	9.8	-84
11.2	10.6	8.9	7.9	7.8	7.8	11.2	9,5
120	11.5	9,8	9.8	8.2	8.2	11.9	10.6
12.7	12.3	10.3	10.2	9,7	9.8	12.5	11.2
13.0	12.8	22.2	10.8	10.3	10.2	24.0	17.5
140	13.6	21.5	12.2	22.2	11.2	14.3	12.4
15.6	14.5	11.9	11.6	11.4	11.9	<u> 14.7</u>	12.7
160	15.4	12.2	12.0	11.9	12.2	15.3	13.4
164	15.6	12.5	12.5	12.3	12.5	15.7	13.6
168	16.9	11.2	133	12.5	14.0	16.2	14.1
17.5	18.3	14.3	14.0	73.9	14.6	16.6	14.4
18,2	19.0	14.7	14.4	14.2	15.3	17.1	14.9
18.7	19.9	14.8	14.6	14.6	15.9	17.4	16.3
19.1	20.8	15.3	14.9	15.3	16.6	18.5	17.2
19.8	21.4	15,7	15.3	15.7	17.Î	19.0	18.2
20.5	21.6	16.2	15.7	16.0	17.5	19.6	19.0
20.9	22.0	26.6	16.5	16.6	18.4	20.0	19.5
21.2	23.0	<u> 17.1</u>	16.6	17.0	18.5	20.4	19.8
21.6	23.3	<u> 17.2</u>	17.2	17.2	19.1	21.0	20.2
21.8		17.2	17.4	<u> 17.5</u>	19.6	21,8	20.5
24.0		18.0	17.8	18.1	20.0	22.5	21.1
		18.5	181	18.5	20.4	23.5	21.6
		19.0	18.6	19.0	20.0		21.9
		19.6	19.0	19,7	21.7		22.2
		20.0	19.6	20.0	22.5		23.6
		20.5	20.0	20.4	23.2		25.1
		27.0	20.5	20.0	23.6		
		21.7	21.1	21.7			
		22.0	21.8	22.4			
		22.4	22.5	22.6			
		22.6	23.5	23.3			
		23.I		23.5			
		23.5					

The peaks underlined are the characteristic peaks among forms A, D,

Family I and Q.

The peaks in italic and underlined are the sets of peaks that are character. within Family I komorphs.

Family I isomorphs have the following common characteristics: the diffraction peaks at 6.2, 11.2, 21.0±0.1 and 22.5±0.1 degree in 2-theta. Each isomorph displays repre- 65 sentative sets of diffraction peaks given in the following, and each set has characteristic spacing between the peaks.

18

The diffraction peak positions reported are accurate to within ±0.2 degree of 2-thete.

A representative FXRD pattern of form A is shown in FIG. 2. Form A displays peaks at 9.3, 13.0 and 18.7 degrees of 2-theta

A representative PXRD pattern of form D is shown in FIG. 6. Form D displays peaks at 3.9, 10.1, 10.6 and 21.4 degrees of 2-theta.

A representative PXRD pattern of Form F is shown in FIG. 10. Form F displays the characteristic peaks of Family I and three sets of peaks, being set 1 at 2-theta of 11.2 and 11.5; sot 2 at 2-theta of 13.9, 14.3, 14.7 and 14.8; sot 3 at 2-thera of 16.2, 16.6, 17.1, 17.2 and 17.7.

A representative PXRD pattern of Form G is shown in FIG. 13. Form G displays the characteristic peaks of Family I and three sets of peaks, being set 1 at 2-theta of 11.2 and 11.6 2; set at 2-theta of 14.0, 14.4, 14.6 and 14.9; set 3 at 2-theta of 16.3, 16.6, 17.2, 17.4 and 17.8.

A representative PXRD pattern of Form J is shown in FIG. 16. Form J displays the characteristic peaks of Family I and three sets of peaks, being set 1 at 2-theta of 11.2 and 11.4; set 2 at 2-theta of 13.9, 14.2 and 14.6; set 3 at 2-theta of 16.0, 16.6, 17.0, 17.2 and 17.5.

A representative PXRD pattern of Form M is shown in FIG. 18. Form M displays the characteristic peaks of Family I and three sets of peaks, being set I at 2-theta of 11.2; set 2 at 2-theta of 14.0 and 14.6; set 3 at 2-theta of 15.9, 16.6, 17.1 and 17.5.

A representative PXRD pattern of Form N is shown in FIG. 10. Form N displays the characteristic peaks of Family I. The sets of peaks of form N are similar to those of forms F, G, J and M, being set 1 at 2-theta of 11.2 to 11.6; set 2 at 2-theta of 13.9 to 15.0; and set 3 at 2-theta of 15.9 to 17.9, with the peaks may vary slightly in position, intensity and width due to mixing of variable proportion of isomorphs in Family I.

A representative PXRD pattern of form Q is shown in FIG. 30. Form Q displays peaks at 2-theta of 6.8, 8.4 and 20.2 degree.

A representative PXRD pattern of form R is shown in FIG. 31.

Example 11

Single Crystal X-ray Analysis

Data were collected at room temperature using Bruker X-ray diffractometers equipped with copper radiation and 50 graphite monochromators. Structures were solved using direct methods. The SHELXTL computer library provided by Bruker AXS, Inc facilitated all necessary crystallographic computations and molecular displays (SHELXTLTM Reference Manual, Version 5.1, Bruker AXS, Madison, Wis., 55 U.S.A. (1997)).

Example 12

Calculation of PXRD Pattern from Single Crystal Date

To compare the results between a single crystal and a powder sample, a calculated powder pattern can be obtained from single crystal results. The XFOG and XPOW computer programs provided as part of the SHELXTL computer library were used to perform this calculation. Comparing the calculated powder pattern with the experimental powder pattern confirms whether a powder sample corresponds to an

19

assigned single crystal structure (Table 9A). This procedure was performed on the crystal forms of azithromycin A, D, F, G, and J.

The calculated PXRD diffraction pattern of azithromycin form A is given in FIG. 1.

The calculated PXRD diffraction pattern of azithromycin form D is given in FIG. 5.

The calculated PXRD diffraction pattern of azithromycin form F is given in FIG. 9.

The calculated PXRD diffraction pattern of azithromycin form G is given in FIG. 12.

The calculated PXRD diffraction pattern of azithromycin form J is given in FIG. 15.

The results are displayed in the overlaid powder X-ray diffraction patterns for forms A, D, F, G, and J in FIGS. 3, 7, 11, 14 and 17, respectively. The lower pattern corresponds to the calculated powder pattern (from single crystal results) and the upper pattern corresponds to a representative experimental powder pattern. A match between the two patterns indicated the agreement between powder sample and the corresponding single crystal structure.

TABLE 9A

	Caciuated and Experimental PKRD Peaks of Isomorphs of Family I						
P cal- culated	Pesperi- mestal	G cal- culated	G expect-	J cal- culated	J experi-	menerj extranj- M	. 3
		5.2	5.0				
		5.7	5.8	5.8	5.7	5.6	
6.3	6.2	6.2	6.2	6.3	6.2	6.2	
7.4	7.4	7.5	7.4	7.4	7.3	7.3	
7.9	7.8	7,9	7.9	7,9	7,8	7.8	3
6.8	8.9	6.9	9.3	8.3	8.2	8.2	
9,9	9.8	9.9	9,9	9.8	9.7	9.8	
10.3	10.3		10.2	10.4	10.3	10.2	
10,9		10.9	10.8	_			
11.3	11.2	11_3	11.2	11.2	11.2	11.2	
11.5	11.4	11.6	11,6	11.4	11.4	missing	4
12.0	11.9	12.0	11.9	12.0	11.9	11.9	
12.3	12.2	12.3		12.3	12.3	12.2	
12_6	12.5	12.5	12.5	12.6	12.5	12.5	
14.0	14.0	13.4	13.3	14.0	13.9	14.0	
14.3	14.3	14.1	14.0	14.2	14.2	mining	
		14.4	14.4			***	-
14.7	14.7	14.7	14,6	14.7	14.6	14.6	
14.9	14.8	14.9	14,9	14.8	450	15.3	
15.4	15.3	15.4	15.3	15.3	15.3	15.9	
15.8	15.7	15.7	15.7	15.8	15.7 16.D	missing	
16.2	16.2	16.3	16.3	16,0	16.6	16.6	
16.6	16.6	16.6	16.6	16,7	10.0 17.0	17.1	
17.1	17.2	17.1		17.1	17.2	Missing 17,1	•
17.3	17.3	17.3	17.2	17.4	17.2	17.5	
17.5	17.4	17.5	17.4	17.6	1/3	1/3	
17.7 18.0	17.7 18.0	17.9 18.1	17.8 18.1	17.9 18.2	18.1	18.4	
104	10.4	10.1					

20

TABLE 9A-continued

	Cactuated and Experimental PXRD Peaks of Isomorphe of Family 1						
Fool- cubied	mentaj Lemen-	G cul- culsted	G experi- mental	i cal-	I caperi- mental	M experi- meals)	
18.6	18.5	18.7	18,7	18.5	18.5	18.5	
19.1	19.0	19.1	19.0	19.1	19.0	19.1	
19.7	19.6	19.6	19.6	19.8	19.7	19,6	
20.0	20.0	20.0	20.0	20.1	20.0	20.0	
20.5	20.4	20.6	20.5	20.5	20.4	20.4	
21.1	21.0	21.2	21.0	20.8	20.9	20.9	
21.8	21.7		21.6	21.6	21.7	21.7	
22.1	22.0	21.8	21.8	21.8			
22.5	22.4	22.3	22.2	22.5	22.4	22.5	
22.7	22.5	22.5	2 2.5	22.6	22.6		
23.1	23.1	22.9		23.4	23.3	23.2	
23.6	23.5	23.5	23.5	23.7	23.5	23.6	

Example 13

Solid State NMR Analysis

Solid State NMR Analysis

All 13C solid state NMR spectra were collected on an 11.75 T spectrometer (Bruker Biospin, Inc., Billerica, Mass.), corresponding to 125 MHz ¹³C frequency. The spectra were collected using a cross-polarization magic 30 angle spinning (CPMAS) probe operating at ambient temperature and pressure. Depending on the quantity of sample analyzed, 7 mm BL or 4 mm BL Bruker probes were employed, accomodating 300 mg and 75 mg of sample with maximum speeds of 7 kHz and 15 kHz, respectively. Data were processed with an exponential line broadening function of 5.0 Hz. Proton decoupling of 65 kHz and 100 kHz were used with the 7 mm and 4 mm probes, respectively. A sufficient number of acquisitions were averaged out to obtain adequate signal-to-noise ratios for all peaks. Typically, 600 scans were acquired with recycle delay of 3.0 s (seconds), corresponding approximately to a 30 minute total acquisition time. Magic angle was adjusted using KBr powder according to standard NMR vendor practices. The spectra were referenced relative to either the methyl resonace of hexamethylbenzen (HMB) at 17.3 ppm or the upfield resonance of adamantane (ADM) at 29.5 ppm. HMB referenced spectra show chemical shifts of all peaks shifted down field by 0.08 ppm with respect to same spectra referenced to ADM. The spectral window minimally included the spectra region from 190 to 0 ppm. The results are summarized in Table 10. Ss-NMR spectra for forms M, H and R were referenced to ADM. Ss-NMR spectra for forms A, D, G, F, J and N were referenced to HMB. Forms H and R were spun at a rate of 15 kHz.

TABLE 10

	¹³ C as NMR chamical shifts of Azithromycin (s0.2 ppm)							
A	D	o	F	1	м	N	Ħ	R
178.1	178.1	179.5	179.5	179.6	177.6	179.6	179.5.	177.9
104.1	103.9	105.5	178.6	178.4	105.6	178.7	178.7	104.6
98.4	95.1	103.5	105.5	105.5	103.4	105.6	105.A	103.6
84.6	84.2	95.0	103.4	103.4	94.9	103.6	103.2	95.3
82.6	79.4	86.2	94.9	95.0	86.7	95.0	95.0	85.4
79.3	78.9	83.1	86,4	86.4	82.9	86.5	86.4	84,0

22

US 6,977,243 B2

21

TABLE 10-continued

	13C ss-NMR chemical shifts of Azithromycin (st).2 pops)							
	ם	G	F	J	м	N	Ħ	R
783 756 747 735 708 680 662 638 632 522 443 426 441, 354 346 265 263	75.7 74.6 74.0 72.9 71.9 71.9 71.0 69.4 67.8 65.7 64.7 49.2 45.8 43.1 40.6 37.1 36.4 29.6	78.9 78.2 77.6 76.4 75.7 74.7 74.3 73.5 71.3 69.8 67.4 65.9 64.0 63.3 50.0 46.0	83.0. 79.1 78.1 77.9 76.5 74.7 74.1 73.5 71.4 69.6 67.3 66.1 65.6 63.6 58.0 47.0 45.9	792 781 762 741 720 713 692 68.6 67.3 68.7 500 46.9 45.9 44.7	79.3 78.1 77.0 76.7 74.7 71.3 69.2 68.6 67.3 66.2 65.5 63.8 63.3 50.0 47.1 45.9 44.7 43.8	N 83.1 79.0 77.9 76.5 74.8 74.2 73.5 69.2 68.7 67.3 66.2 65.7 63.7 63.1 47.1 47.1 46.0 44.8	82.7 78.2 78.3 78.0 76.4 74.1 73.5 73.1 72.1 68.4 61.3 65.5 63.7° 49.9 46.8	79,4 79,0 75,6 74,5 73,9 73,9 71,8 71,0 69,1 67,5 65,5 64,5 49,4 45,7 42,9 41,6 40,4
263 233 21.7 21.7 19.5 17.3 15.2 11.3 7.2	28.0 22.1 22.1 18.6 16.7 16.1 10.6 9.0 8.6	46.0 44.7 41.5 40.8 37.5 36.5 33.6 27.9 23.1 22.5 20.9 20.9 20.9 20.9 20.9 20.9 20.9 20.9	45.9 44.7 41.5 41.1 37.3 36.6 30.3 28.0 27.1 23.2 22.6 20.8 20.8 20.8 16.8 17.2 19.1 9.8 17.2 19.3 19.5 1	44.7 43.7 41.6 41.0 37.1 35.8*** 33.5 30.4 28.0 27.1 25.2 21.9** 20.7 18.9 16.8 12.1 12.1 10.0 1	41.8 41.1 37.4 30.6 30.1 27.2 26.2 22.8 22.5 22.5 22.5 20.2 18.9 17.4 16.3 15.5 12.1 10.3 	44.8 43.5 41.1 37.3 36.5 33.7 30.4 28.1 27.2 22.0 22.8 19.0 20.8 19.9 15.8 12.2 9.9 15.8 17.9 6.6	46.8 44.5 43.8* 40.9 37.1 36.3 33.7 27.9 27.1 22.6 22.9 20.7 20.7 20.8 17.1 16.6 15.8 15.4 12.0 9.9 17.1 16.7 17.1 17.1 17.1 17.1 17.1 17.1	37.0 36.2 29.4 29.0 28.2 27.4 21.4 21.4 16.1 15.7 10.3 8.9 8.9 8.9

The chemical shifts labeled in bold and underlined are the peaks or sets of peaks representative of seek form. The chemical shifts labeled in tails are the solvent peaks that may be broad and variable (a0.4 ppm), The chemical shifts labeled with single saterisk may abow apliting of od.3 ppm. The chemical shifts labeled with double saterisks may show variation of x0.3 ppm.

The chemical shifts reported are accurate to within ±0.2 ppm unless otherwise indicated.

Arepresentative ¹³C ssNMR spectrum of form A is shown in FIG. 21. Form A displays a peak at 178.1 ppm, and peaks at 104.1, 98.4, 84.6, 26.9, 13.2, 11.3 and 7.2 ppm.

A representative ¹³C ssNMR spectrum of form D is shown in FIG, 22. Form D displays the highest chemical shift peak of 178.1 ppm and peaks at chemical shifts of 103.9, 95.1, 84.2, 10.6, 9.0 and 8.6 ppm.

Are presentative ¹³C ssNMR spectrum of form F is shown on FIG. 23. Form F has two chemical shift peaks at approximately 179.1±2 ppm, being 179.5 ppm and 178.6 ppm, and a set of 5 peaks at 10.1, 9.8, 9.3, 7.9, and 6.6 ppm, and ethanol peaks at 58.0±0.5 ppm and 17.2±0.5 ppm. The solvent peaks can be broad and relatively weak in intensity.

A representative ¹³C saNMR spectrum of form G is shown in FIG. 24. Form G has the highest chemical shift

peak of 179.5 ppm, being a single peak with possible splitting of <0.3 ppm and a set of 5 peaks at 10.4, 9.9, 9.3, 7.6, 6.5 ppm.

A representative ¹³C ssNMR spectrum of form J is shown in FIG. 25. Form J has two chemical shift peaks at approximately 179.1±2 ppm, those being 179.6 ppm and 179.4 ppm, a set of 4 peaks at 10.0, 9.3, 8.1 and 6.8 ppm and n-propanol peaks at 11.5±0.5 ppm and 25.2±0.5 ppm. The solvent peak can be broad and relatively weak in intensity.

A representative ¹³C sxNMR spectrum of form M is shown in FIG. 26. Form M has one chemical shift peak at 179±1 ppm, being 179.6 ppm, peaks at 41.9, and 16.3 ppm, a set of 5 peaks at 10.3, 9.6, 9.3, 7.7 and 7.1 ppm and an isopropanol peak at 26.0±0.5 ppm. The solvent peak can be broad and relatively weak in intensity.

A representative ¹³C ssNMR spectrum of form N is shown in FIG. 27. Form N displays chemical shifts as a

US 6.977.243 B2

23

combination of isomorphs in Family I. The peaks may vary in chemical shift and in relative intensities and width due to the mixing of variable proportion of isomorphs contained in the form N crystalline solid solution.

A representative 13C scNMR spectrum of amorphous 5 form is shown in FIG. 28. The amorphous azithromycin displays broad chemical shifts. The characteristic chemical shifts have the peak positions at 179 and 11±0.5 ppm.

A summary of the observed saNMR peaks for forms A, D,

Example 14

NMR Analysis of a Dosage Form

To demonstrate the ability of 13C saNMR to identify the form of azithromycin contained in a pharmaceutical dosage form, coated azithromycin tablets containing form G azithromycin were prepared and analyzed by ¹³C ssNMR. Tablets were wet granulated and tabletted on an F-Press 20 (Manesty, Liverpool, UK) using 0.262"x0.531" tooling. Tablets were formulated and tabletted to contain 250 mg of form G azithromycio with a total tablet weight of 450 mg using the formula given below. The tablets were uniformly coated with pink Opadry II (mixture of lactose 25 monohydrate, hydroxypropylmethylcellulose, titanium dioxide, Drug & Cosmetic red #30, and triacetin) (Colorcon, West Point, Pa.).

Matorial	Percentage	Batth(g)
Azithromycia form "O"	58.23	174.69
Pregeliatinized oora starch	6,00	18,00
Anhydrous dicalcium phosphais	30.85	92.55
Sodium croecarmelose	2.00	6.00
Magazzinen stearste with 10% sodium hunel guifate	292	8.76
nichief entrare		
Total	100.00	300.00

A coated tablet was gently crushed and the powdered sample was packed with a packing tool in solid state rotor containing no 13C background. Analysis of the sample was performed under conditions outlined in Example 13.

A representative 13C saNMR spectrum of the tablet containing form G azithromycin is given in FIG. 29.

Example 15

Antimicrobial Activity

The activity of the crystal forms of the present invention against bacterial and protozoa pathogens is demonstrated by the compound's ability to inhibit growth of defined strains of human (Assay I) or animal (Assays II and II) pathogens.

Assay I

Assay I, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to com- 60 pounds that circumvent defined mechanisms of macrolide resistance. In Assay I, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of macrolide resistance mechanisms that have been characterized. Use of this panel enables 65 the chemical structure/activity relationship to be determined with respect to potency, spectrum of activity, and structural

elements or modifications that may be necessary to obviate resistance mechanisms. Bacterial pathogens that comprise the screening panel are shown in the table below. In many cases, both the macrolide-susceptible parent strain and the macrolide-resistant strain derived from it are available to provide a more accurate assessment of the compound's ability to circumvent the resistance mechanism. Strains that contain the gene with the designation of ermA/ermB/ermC are resistant to macrolides, lincosamides, and streptogramin F, G, H, J, M, N and R azithromycin is given in Table 10. 10 B antibiotics due to modifications (methylation) of 23S rRNA molecules by an Erm methylase, thereby generally prevent the binding of all three structural classes. Two types of macrolide efflux have been described; marA encodes a component of an efflux system in staphylococci that pre-15 vents the entry of macrolides and streptogramins while mefA/E encodes a transmembrane protein that appears to efflux only macrolides. Inactivation of macrolide antibiotics can occur and can be mediated by either a phosphorylation of the 2'-hydroxyl (mph) or by cleavage of the macrocyclic lactone (esterase). The strains may be characterized using conventional polymerase chain reaction (PCR) technology and/or by sequencing the resistance determinant. The use of PCR technology in this application is described in J. Sutcliffe et al., "Detection Of Erythromycin-Resistant Determinants By PCR", Antimicrobial Agents and Chemotherapy, 40(11), 2562-2566 (1996). The assay is parformed in microtiter trays and interpreted according to Performance Standards for Antimicrobial Disk Susceptibility Tests—Sixth Edition; Approved Standard, published by The National 30 Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. The crystalline compound is initially dissolved in dimethylsulfoxide (DMSO) as 40 mg/ml stock solution.

Strain Durignation	Macrolide Resistance Mechanism(s)
Staphylococcus aureus 1116	succeptible parent
Stephylococcus sureus 1117	ErmB
Staphylococcus aureus 0052	susceptible parent
Staphylococcus aureus 1120	EranC
Staphylococcus sureus 1032	merA, mph, esterase
Staphylococcus hemolyticus 1006	merA, mph
Streptococcus pyogenes 0203	statoophbio parent
Streptococcus pyogenes 1079	ErmB
Streptococcus pyogenes 1062	sosceptible parent
Streptococcus pyogenes 1061	EmB
Streptococcus pyogenes 1064	EmB
Streptococcus agulecties 1024	susceptible purent
Streptococcus againesine 1023	ErmB
Streptococcus pneumonine 1016	Susceptible
Streptococcus pneumoniae 1046	EmB
Streptococcus preumoniae 1095	RepuB
Streptococcus presentarios 1175	MeiB
Streptococcus pneumonlae 0085	Susceptible
Heanophilus influenzae 0131	Susceptible
Morecella caterrhalis 0040	Susceptible
Moraxella catarrhalis 1055	erythromycia intermediate resistance
Escherichia coll 0266	Susceptible

Assay II is utilized to test for activity against Pasteurella multocida and Assay III is utilized to test for activity against Pasteurella haemolytica.

Assay II

This assay is based on the liquid dilution method in microliter format. A single colony of P. multocida (strain 59A067) is inoculated into 5 ml of brain heart infusion (BHI) broth. The test compound is prepared by solubilizing

25

1 mg of the compound in 125 µl of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated BHI broth. The concentrations of the test compound used range from 200 µg/ml to 0.098 µg/ml by two-fold serial dilutions. The P. multocida inoculated BHI is 5 diluted with uninoculated BHI broth to make a 10⁴ cell suspension per 200 µl. The BHI cell suspensions are mixed with respective serial dilutions of the test compound, and incubated at 37° C, for 18 hours. The minimum inhibitory concentration (MIC) is equal to the concentration of the 10 compound exhibiting 100% inhibition of growth of P. multocida as determined by comparison with an uninoculated control.

Assay III

This assay is based on the agar dilution method using a Steem Replicator. Two to five colonies isolated from an agar plate are inoculated into BHI broth and incubated overnight at 37° C. with shaking (200 rpm). The next morning, 300 μ l of the fully grown P. haemolytica preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37° C, with shaking (200 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two mi of the respective serial dilution is mixed with 18 ml of molten BHI agar and solidified. When the inoculated P. haemolytica culture reaches 0.5 McFarland standard density, about 5 μ l of the P. haemolytica culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and incubated for 18 hours at 37° C. Initial concentrations of the test compound range from 100-200 µg/ml. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of P. haemolytica as determined by comparison with an uninocu-

The in vivo activity of the crystal forms of the present invention can be determined by conventional animal protection studies well known to those skilled in the art, usually carried out in mice.

Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Animals are inoculated with 0.5 ml of a 3×103 CFU/ml bacterial suspension (P. multocida atrain 59A006) intraperitoneally. Each experiment has at least 3 nonmedicated control groups including one infected with 0.1× challenge dose and two infected with 1x challenge dose; a 10x challenge data group may also be used. Generally, all mice in a given study can be challenged within 30-90 minutes, especially if a repeating syringe (such as a Com- 50 wall@ syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of 30 minutes. The routes of admin- 55 istration are subcutaneous or oral doses. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. Compounds are administered 30 minutes, 4 hours, and 24 hours after challenge. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded. The P. multocida model monitoring continues for 96 hours (four days) post challenge.

The PD_{50} is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due

26

to the bacterial infection that would be lethal in the absence of drug treatment.

The crystal forms of the present invention (hereinafter "the active compound(s)"), may be administered through oral, parenteral, topical, or rectal routes in the treatment or prevention of bacterial or protozoa infections. In general, the active compound is most desirably administered in dosages ranging from about 0.2 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 2 mg/kg/day to about 50 mg/kg/day 15 is most desirably employed. Variations may nevertheless occur depending upon the species of mammal, fish or bird being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compound may be administered alone or in combination with pharmaceutically acceptable carriers or difuents by the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the active compound may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, 36 jellies, gels, pastes, lotions, ointments, sachets, powders for oral suspension, aqueous suspensions, injectable solutions, clixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compound is present in such dosage forms at concentration levels ranging from about 1.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline collulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably com, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and tale are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or clixirs are desired for oral administration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations

For parenteral administration, solutions of the active 65 compound in either sesame or peannt oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if

27

necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and aubcutaneous injection purposes. The preparation of all these solutions under sterile 5 conditions is readily accomplished by standard pharmaceutical techniques will known to those skilled in the art.

Additionally, it is also possible to administer the active compound topically and this may be done by way of creams, jellies, gels, pastes, patches, cintments and the like, in 10 accordance with standard pharmaceutical practice.

For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

The active compound may also be administered in the form of liposome delivery systems, such as small unitamellar vosicles, large unilamellar vosicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

What is claimed is:

- 1. A crystalline form of azithromycin according to claim 20 wherein said azithromycin comprises more than 50% by 25 weight of azithromycin sesquihydrate.
- 2. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 55% or more by weight of azithromycin sesquihydrate.
- 3. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 60% or more by weight azithromycin sesquihydrate.
- 4. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 65% or more by weight of azithromycin sesquihydrate.
- 5. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 70% or more by weight of azithromycin sesquihydrate.
- 6. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 75% or more by 40 weight of azithromycin sesquihydrate.
- 7. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 80% or more by weight of azithromycin sesquihydrate.
- 8. A crystalline form of azithromycin according to claim 45 1, wherein said azithromycin comprises 85% or more by weight of azithromycin sesquihydrate.
- 9. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 90% or more by weight of azithromycin sesquihydrate.

28

- · 10. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 91% or more by weight of azithromycin sesquihydrate.
- 11. A crystalline form of azithromycln according to claim 1, wherein said azithromycin comprises 92% or more by weight of azithromycin sesquihydrate.
- 12. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 93% or more by weight of azithromycin cesquihydrate.
- 13. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 94% or more by weight of azithromycin sesquihydrate.
- 14. A crystalline form of azithromycin according to claim 15 1, wherein said azithromycin comprises 95% or more by weight of azithromycin sesquihydrate.
 - 15. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 96% or more by weight of azithromycin sesquihydrate.
 - 16. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 97% or more by weight of azithromycle sesquihydrate.
 - 17. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 98% or more by
 - 18. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 99% or more by weight of azithromycin sesquihydrate.
- 19. A crystalline form of szithromycin according to claim 1 wherein said azithromycin comprises 99% or more by weight of azithromycin acsquihydrate.
- 20. The crystalling form of azithromycin according to claim I wherein said 13C solid stat NMR spectrum further comprising a peak with chemical shift of about 10.4 ppm.
- 21. The crystalline form of azithromycin according to claim 20 wherein said 13 C solid state NMR spectrum further comprising a peak with chemical shift of about 9.9 ppm.
- 22. The crystalline form of azithromycin according to claim 21 wherein said 12 C solid state NMR spectrum further comprising a peak with chemical shift of about 9.3 ppm.
- 23. The crystalline form of azithromycin according to claim 22 wherein said 13 C solid state NMR spectrum further comprising a peak with chemical shift of about 7.6 ppm.
- 24. The crystalline form of azithromycin according to claim 23 wherein said 13 C solid state NMR spectrum further comprising a peak with chemical shift of about 6.5 ppm.

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 6,977,243 B2 DATED

: December 20, 2005

INVENTOR(S) : Li et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27, line 23 - Column 28, line 47,

Replace claims 1-24 with the following:

- 1. A crystalline form of azithromycin which is azithromycin sesquihydrate being characterized as having a ¹⁷C solid state NMR spectrum comprising a plurality of peaks with at least one peak having a chamical shift of about 179.5 ppm.
- 2. A crystalline form of exithromyoin according to claim 1 wherein said azithromyoin comprises more than 50% by weight of azithromycin sesquihydrate.
- A crystalline form of azitimomycin according to claim 2, wherein said azitimomycin comprises
 or more by weight of azitimomycin according to claim 2, wherein said azitimomycin according to claim 2.
- 4. A crystalline form of azithromycin according to claim 2, wherein seld azithromycin comprises 60% or more by weight of azithromycin sasquiltydrate.
- A crystalline form of exithromyoin according to claim 2, wherein said exithromyoin comprises
 or more by weight of exithromyoin sesquihydrate.
- 6. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 70% or more by weight of azithromycin seaquiliyoʻrate.
- 7. A crystalline form of azilhromycin according to claim 2, wherein said azilhromycin comprises 75% or more by weight of azithromycln sesquiltydrate.
- 8. A crystailine form of azithromycin according to claim 2, wherein said azithromycin comprises 80% or more by weight of azithromycln sesquinydrate.
- A crystelline form of extitromycin according to claim 2, wherein said aziltromycin comprises
 or more by weight of aziltromycin assquiltydrate.
- 10. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 90% or more by weight of azithromycin assquitydrate.
- 11, A crystalline form of szithromych according to claim 2, wherein said szithromycin comprises 81% or more by weight of azithromycin sesquihydrate.
- 12. A crystallins form of szithromycin according to claim 2, wherein said szithromycin comprises 92% or more by weight of azithromycin sesquihydrate.
- 13. A crystalline form of exithromycin according to claim 2, wherein said exittromycin comprises 93% or more by weight of azithromycln sesquinydrate.
- 14. A crystaline form of azithromych according to claim 2, wherein said azithromych comprises 94% or more by weight of azillatomycin sesquilydrate.
- 15. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 95% or more by weight of azithromycin assquihydrale.
- 16. A crystalline form of azithromycin according to cialm 2, wherein said azithromycin comprises 96% or more by weight of azithromycin seacultydrate.
- 17. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 97% or more by weight of azithtomycin sesquinydrate.
- 18. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 98% or more by weight of ezithromycln sesquihydrate.

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 6,977,243 B2 DATED

: December 20, 2005

Page 2 of 2

INVENTOR(S) : Li et al.

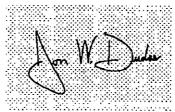
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27, line 23 - Column 28, line 47 (cont'd),

- 19. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 99% or more by weight of azithromycin sesquihydrate.
- 20. The crystatilne form of azithromycin according to claim 1 wherein said 14C solid state NMR spectrum further comprising a peak with chemical shift of about 10,4 ppm.
- 21. The crystallins form of szithromycin according to claim 20 wherein said 13C solid state NMR spectrum further comprising a peak with chemical shift of about 9.9 ppm.
- 22. The crystalline form of szithromycin according to claim 21 wherein said 12 C solid state NMR spectrum further comprising a peak with chemical shift of about 9.3 ppm.
- 23. The crystelline form of azithromycin according to claim 22 wherein said ¹³C solid state NMR spectrum further comprising a peak with chemical shift of about 7.6 ppm.
- 24. The crystatine form of existromyon according to claim 23 wherein said ¹²C solid state NMR spectrum further comprising a peak with chamical shift of about 6.5 ppm.

Signed and Sealed this

Seventh Day of February, 2006



JON W. DUDAS Director of the United States Patent and Trademark Office

EXHIBIT H



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Consumer Health Care: Morris Plains, New Jersey

Web Site Address: http://www.pfizer.com

Stock Exchange Listings: New York Stock Exchange (PFE)

London (PFZ) Euronext Swiss

2005 Revenues: \$51.3 Billion

2005 Actual R&D Spending: \$7.4 Billion

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Norvasco (amiodipine besylate) Viagrao (sildenafil citrate) tablets Xalatano (latanoprost ophthalmic

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* Aricepte is a registered trademark of Eisai Co., Ltd.

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Last Update: January 24, 2006

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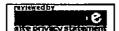


EXHIBIT I

SEP 2 3 2002

- 104-Q5-0V

Attorney Docket No. PC11724A

Patent Application U.S. Serial No. 10/152,106

THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: A. TRASK

Examiner: Not Yet Assigned APPLICATION SERIAL NO.: 10/152,106

Group Art Unit: 1623 FILING DATE: MAY 21, 2002

CRYSTAL FORMS OF TITLE: AZITHROMYCIN

COMMISSIONER FOR PATENTS WASHINGTON, D.C. 20231

Sir:

1

PRELIMINARY AMENDMENT

Prior to examination on the merits, please amend the above-identified application as follows:

In the Specification:

On page 1, after the title, please insert the following: 1-This application claims the benefit of U.S. Provisional Application Serial No. 60/292,565, filed May 22, 2001; U.S. Provisional Application Serial No. 60/297,741, filed June 12, 2001; and U.S. Provisional Application Serial No. 60/343,041, filed December 21, 2001, the contents of the aforementioned provisional patent applications are hereby incorporated by reference in their entirety .--

The above amendment adds no new matter to this application. Applicants respectfully request its entry.

REMARKS

Applicants have amended the specification to include priority data as required pursuant 37 C.F.R. §1.78.

Applicants respectfully submit that no new matter is added to the present application.

Applicants have attached hereto a marked-up version of the changes made to the specification by the current amendment. The attached marked-up version is labeled "Version with Markings to Show Changes Made - Do Not Enter". The marked-up version can be found following the signature page of this Amendment.

A favorable response is requested RECEIVED

USERS/DOCS/LA21952/LPAGL/40, X01LDOC / 187521

SEP 2 7 2002

Express Mail No. EL162816349 US

TECH CENTER 1600/2900



Patent Application Attorney Docket No. PC11724A U.S. Serial No. 10/152,106

-2-

Date: September 23, 2002

Pfizer Inc Patent Department, 5th Floor 150 East 42nd Street New York, NY 10017-5755 (212) 733-1038 Respectfully submitted,

Adrian G. Looney Attorney for Applicants Reg. No. 41,406

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SEP 2 7 2002

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Express Mail No. EL162816349 US

a

Patent Application

Attorney Docket No. PC11724A U.S. Serial No. 10/152,106

VERSION WITH MARKINGS TO SHOW CHANGES MADE - DO NOT ENTER

-3-

In the Specification

The following sentence containing the priority application data for the subject application has been added following the Title of the application on page 1 as follows: "This application claims the benefit of U.S. Provisional Application Serial No. 60/292,565, filed May 22, 2001; U.S. Provisional Application Serial No. 60/297,741, filed June 12, 2001; and U.S. Provisional Application Serial No. 60/343,041, filed December 21, 2001, the contents of the aforementioned provisional patent applications are hereby incorporated by reference in their entirety."

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JAN 1 8 2006

PATENT Attorney Docket No. PC11714A US

Office of Patent Publication
Director's Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Certificate of Correction Branch Commissioner for Patents P. O. Box 1450-Alexandria, VA 22313-1450

REQUEST FOR EXPEDITED ISSUANCE OF A CERTIFICATE OF CORRECTION UNDER 37 C.F.R. §1.322 AND M.P.E.P. §1480.01

Dear Sir.

Patentee respectfully requests an expedited issuance of a Certificate of Correction under M.P.E.P §1480.01 to correct errors attributable to the United States Patent and Trademark Office, which are identified on Certificate of Correction form PTO/SB/44 enclosed herewith.

Patentee further requests that the Patent Office disregard the Certificate of Correction filed on January 6, 2006 which did not correct all of the errors in the patent.

No fee should be required for this request since the errors are due to the USPTO. Notably, the August 31, 2005 Index of Claims indicates that allowed claim 125 should be claim 1 in the issued patent and this claim was actually omitted in the issued patent. Moreover, the Index of Claims also indicates that allowed claims 36 - 53 should be claims 2-19 in the issued patent, not claims 1-18 as actually printed. Claims 20 - 24 in the issued patent (which

PATENT Attorney Docket No. PC11724A US

correspond to allowed claims 126-130) were numbered correctly. For your convenience, a copy of the August 31, 2005 Index of Claims, a copy of the issued claims as well as the Notice of Allowability and the pending claims before the issuance of the Notice of Allowance (i.e., from the Amendment filed on June 6, 2005) are enclosed.

The incorrect numbering of many of the claims in the patent has led to errors in the dependencies of many of the claims. These errors have also been corrected in the attached Certificate of Correction.

Patentee has also noticed that in the Examiner's amendment that was a part of the Notice of Allowability dated August 31, 2005, the Examiner's amendment to claim 125, line 3, appears to have added a second "with" to line 3 so that the language reads "with with at least one peak...". This is clearly an inadvertent error on the Examiner's part. Accordingly, Patentee has also corrected this obvious error in the attached Certificate of Correction.

Furthermore, the allowed claim 126 spells the words "crystalline" and "state" correctly although these words were misspelled in claim 20 of the issued patent as "crystalling" and "stat," respectively. Finally, in allowed claim 128, reference was made correctly to "13C" solid state NMR although claim 22 of the patent refers incorrectly to "12C" solid state NMR.

In view of the large number of errors in the claims of the patent, Patentee believes that that the easiest way to correct all of the errors is to submit a substitute set of claims for the patent. This substitute set of claims appears in the attached Certificate of Correction (form PTO/SB/44).

It is respectfully submitted that all of the errors that have been corrected in the substitute set of claims in the attached Certificate of Correction were made by the United States Patent and

PATENT Attorney Docket No. PC11724A US

Trademark Office. Accordingly, Patentee respectfully requests that a Certificate of Correction be issued on an expedited basis under M.P.E.P. § 1480.01.

No fee is believed to be necessary in connection with the filing of this Certificate of Correction. If, however, the Commissioner determines that any fee is due, the Commissioner is hereby authorized to charge any such fees, which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Respectfully submitted,

Date: Jar 18, 2006

Lance Y. Liu
Attorney for Patentee
Reg. No. 45,379

Customer No. 28523
Pfizer Inc.
Patent Department, MS 8260-1611
Eastern Point Road
Groton, Connecticut 06340
(860) 686-1652

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 2

PATENT NO.

6,977,243

APPLICATION NO. :

10/152,108

ISSUE DATE

December 20, 2005

INVENTOR(S)

Zheng J. Li and Andrew V. Trask

It is cartified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Please replace claims 1 - 24 of the patent with the following set of corrected claims:

- 1. A crystalline form of azithromycin which is azithromycin sesquihydrate being characterized as having a ¹³C solid state NMR spectrum comprising a plurality of peaks with at least one peak having a chemical shift of about 179.5 ppm.
- 2. A crystalline form of azithromycin according to claim 1 wherein said azithromycin comprises more than 50% by weight of azithromycin sesquihydrate.
- 3. A crystaltine form of azithromycin according to claim 2, wherein said azithromycin comprises 55% or more by weight of azithromycln sesquihydrate.
- 4. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 60% or more by weight of azithromycin sesquihydrate.
- 5. A crystalline form of azithromycln according to claim 2, wherein said azithromycln comprises 65% or more by weight of azithromycin sesquiltydrate.
- 6. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 70% or more by weight of azithromycin sesquinydrate.
- 7. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 75% or more by weight of azithromycln sesquihydrate.
- 8. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 80% or more by weight of azithromycin sesquihydrate.
- 9. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 85% or more by weight of azithromycln sesquihydrate.
- 10. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 90% or more by weight of azithromycln sesquihydrate.
- 11. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 91% or more by weight of azilthromycin sesquihydrate.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Lance Y. Liu, Pfizer, Inc., Patent Department, MS 8260-1611

Eastern Point Road, Groton, Connecticut 06340

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 2 of 2

PATENT NO.

6,977,243

APPLICATION NO.

10/152.106

ISSUE DATE

December 20, 2005

INVENTOR(S)

Zheng J. Li and Andrew V. Trask

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(corrected set of claims continued from page 1)

- 12. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 92% or more by weight of azithromycin sesquihydrate.
- 13. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 93% or more by weight of azithromycin sesquihydrate.
- 14. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 94% or more by weight of azilhromycin sesquihydrate.
- 15. A crystalline form of azithromycln according to claim 2, wherein said azithromycln comprises 95% or more by weight of azithromycin sesquihydrate.
- A crystalline form of ezithromycln eccording to claim 2, wherein said ezithromycln comprises. 95% or more by weight of azithromych sesquihydrate.
- 17. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 97% or more by weight of azithromycin sesquihydrate.
- 18. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 98% or more by weight of azithromycin sesquihydrate.
- 19. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 99% or more by weight of azithromycin sesquihydrate.
- 20. The crystalline form of azithromycin according to claim 1 wherein said 13C solid state NMR spectrum further comprising a peak with chemical shift of about 10,4 ppm.
- 21. The crystatline form of azithromycln according to claim 20 wherein said 19C solid state NMR spectrum further comprising a peak with chemical shift of about 9.9 ppm.
- 22. The crystalline form of azithromycin according to claim 21 wherein said 13C solid state NMR spectrum further comprising a peak with chemical shift of about 9.3 ppm.
- 23. The crystalline form of szithromycin according to claim 22 wherein said ¹³C solid state NMR spectrum further comprising a peak with chemical shift of about 7.6 ppm.
- 24. The crystalline form of azithromycin according to claim 23 wherein said ¹³C solid state NMR spectrum further comprising a peak with chemical shift of about 6.5 ppm.

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Lance Y. Liu,

Pfizer, Inc., Patent Department, MS 8260-1611

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